

STUDIES OF NEW CYCLISATION REACTIONS
OF HETEROAROMATIC NITRO AND NITROSO
COMPOUNDS

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Thesis presented for the Degree of Doctor of Philosophy

University of Edinburgh

1985



DECLARATION

I declare that this thesis is my own composition, that the work of which it is a record has been carried out by myself and that it has not been submitted in any previous application for a Higher Degree.

The thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr. G. Tennant between October 1980 and September 1983.

ACKNOWLEDGEMENTS

I should like to thank Dr. G. Tennant for his encouragement and supervision provided during the course of my research work.

I should also like to thank Lyonnaise Industrielle Pharmaceutique (LIPHA), 34 Rue Saint-Romain, Lyon, France for their financial support over the three years. I am also grateful to the University of Edinburgh for the provision of laboratory and library facilities. I am further indebted to the technical staff of the Department of Chemistry, University of Edinburgh, notably Mr. L. Bell, Mr. J. Millar, and Mr. D. Thomas for the measurement of ^1H and ^{13}C n.m.r. spectra and mass spectra recorded in this thesis.

I should also like to acknowledge Dr. E. Szarvasi, (LIPHA) for his many helpful suggestions and interest in the research carried out in collaboration with LIPHA.

I should also like to thank Mrs. C. Ranken for her care and patience in typing the manuscript of this thesis.

POSTGRADUATE LECTURE COURSES ATTENDED BETWEEN OCTOBER 1980
AND SEPTEMBER 1983

"Current topics in Organic Chemistry 1980",
Dr. A.J. Bellamy et al., University of Edinburgh.

"Reactive Intermediates",
Dr. J.T. Sharp, University of Edinburgh.

"Molecular Interactions in Industrial Food Research",
Staff of Unilever Research, Colworth Laboratory.

"Bio-organic Chemistry",
Dr. R. Baxter et al., University of Edinburgh.

"Synthesis and Mechanism of Action of the β -Lactam Antibiotics",
Staff of Glaxo Group Research Limited (Greenford).

"Current topics in Organic Chemistry 1982",
Dr. H. McNab et al., University of Edinburgh.

"1,3-Dipolar Intermediates in Heterocyclic Synthesis",
Dr. R.M. Paton and Dr. J.T. Sharp, University of Edinburgh.
Organic Research Group Seminars, 1980-81, 1981-82, and
1982-83.

Royal Society of Chemistry - Perkin Division 9th, 10th and
11th Scottish Regional Meetings.

Royal Society of Chemistry - Perkin Division, 1982 Autumn
Meeting - Heriot Watt University.

ABSTRACT

The subject matter of this thesis is concerned with investigations into the synthesis of N-oxygenated polyazaheterocyclic systems. In particular base-catalysed cyclisation reactions of suitably substituted ortho-nitroimidazoles, ortho-nitrosopyrazoles and 2,4-dinitrobenzene derivatives were investigated for the synthesis of N-oxygenated purines, pteridines and 'stretched' analogues, and N-oxygenated pyrazolopyrazines. The description of the results obtained in these studies is preceded by a review on the scope and mechanism of cyclisation reactions of nitro and nitroso compounds known to give N-oxygenated polyazaheterocyclic products.

The synthesis of N-substituted imidazolyldicarboxamides, potentially capable of undergoing base-catalysed cyclisation to purine N-oxides were readily accomplished. However the attempted base-catalysed cyclisation of these substrates failed to give the anticipated purine N-oxide products, the main products isolated being imidazole derivatives derived by side-chain hydrolysis. The attempted cyclisation of a readily prepared ortho-nitroimidazolyldiazine derivative also failed to give an N-oxygenated heterocyclic product. The reaction of amino-nitroimidazole derivatives with acid chlorides was investigated and the reactivity of the resulting α -substituted nitroimidazolyl acetamides towards base-catalysed cyclisation investigated. The only products isolated in these reactions were imidazole derivatives resulting from side-chain hydrolysis of the acetamido-substituent. The

preparation of suitably ortho-substituted nitropyridazines was moderately successful, but attempts to cyclise such compounds to N-oxygenated imidazopyridazines or N-oxygenated triazolopyridazines gave only intractable mixtures.

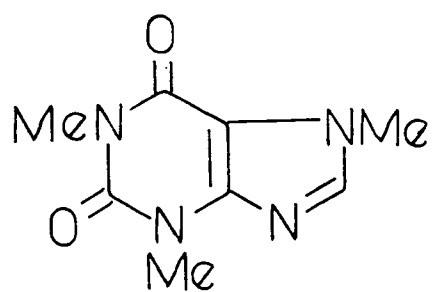
The reaction of ortho-amino-nitrosopyrazole derivatives with carboxylic acid chlorides or with carboxylic acids in the presence of dicyclohexylcarbodiimide gave the expected acetamido derivatives. However the base-catalysed cyclisation of these failed to give the expected pyrazolopyrazine N-oxides, the observed products being the parent pyrazolopyrazines. The synthesis of pyrazolylurea derivatives by reaction of amino-nitrosopyrazoles with isocyanates was unsuccessful, the products being novel pyrazolo-oxadiazine derivatives. The behaviour of the pyrazolo-oxadiazinones so obtained, towards ring-opening reactions with primary and secondary amines, hydrazines and carbanionic reagents was investigated.

The attempted synthesis of ortho-chloro-nitrobenzimidazole derivatives and ortho-chloro-nitroquinazoline derivatives suitable for further elaboration to 'stretched' purines and pteridine N-oxides was largely unsuccessful. On the other hand treatment of readily prepared ortho-chloro-nitroquinoxalinone derivatives with benzylamine, followed by base-catalysed cyclisation provided a practical synthesis of previously unknown N-hydroxyimidazoquinoxalinone derivatives. Acylation of readily synthesised ortho-amino-nitroquinoxalinones, followed by base-catalysed cyclisation of the resulting amides gave either the expected pyrazinoquinoxalinone N-oxides or ring-contracted imidazoquinoxalinones.

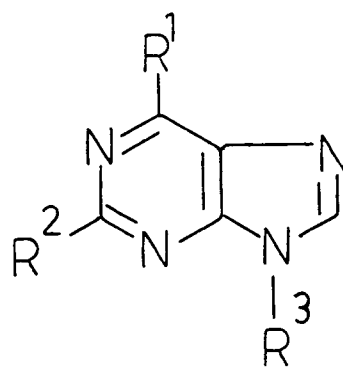
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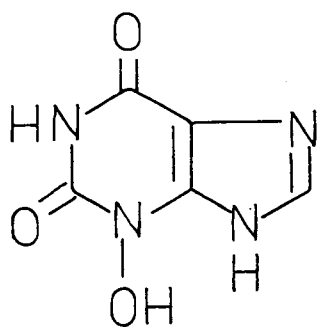


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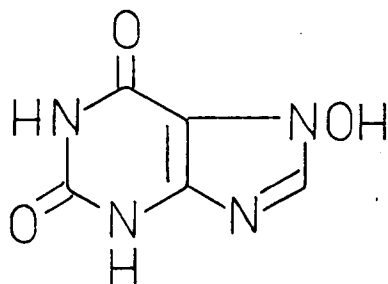


(2)	<u>R¹</u>	<u>R²</u>	<u>R³</u>
a;	NH ₂	H	H
b;	Cl	H	H
c;	Cl	H	Me
d;	SH	NH ₂	H
e;	NH ₂	NH ₂	H

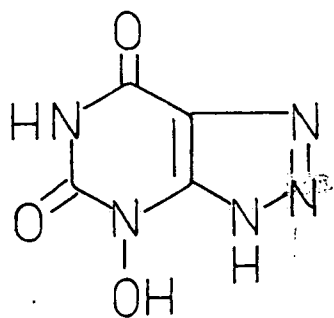
Scheme 1



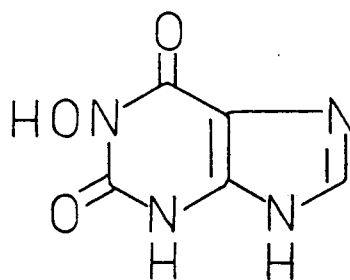
(3)



(4)



(5)



(6)

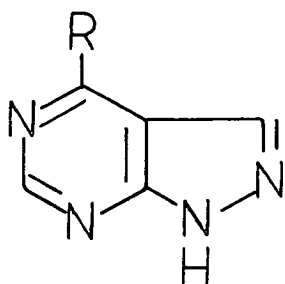
Scheme 2

FOREWORD

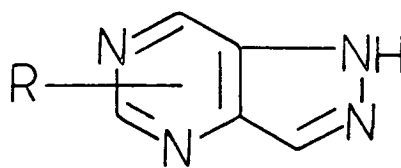
The following thesis describes investigations into new, general synthetic approaches to purine and pteridine N-oxides and their azalogues and isosteres. The stimulus for these synthetic studies was the well known biological activity of purine and pteridine derivatives in general, and their lesser known N-oxygenated derivatives in particular.

Purines (Scheme 1) are known to play a fundamental role in the chemistry of nucleic acids and in cellular biochemistry. Investigations into their chemotherapeutic properties started as early as 1935.¹ The diuretic properties of caffeine (1)² and methylated xanthines³ were reported as early as 1900 and it has been shown⁴ that adenine (2a) has a marked oral diuretic effect.

It has been demonstrated⁵ that certain purinones show antitumour activity in animals, although the biochemical mechanism of this activity is not certain. 6-Chloropurine (2b) has also been shown⁶ to exhibit activity against tumours in animals and human leukaemia and this activity is enhanced in the 9-methyl derivative (2c).⁷ 2-Aminopurine-6-thiol (2d) was also shown to be a potent inhibitor of human leukaemia⁸ but its toxicity severely limits its clinical viability. This compound also showed significant antiviral activity in vivo⁹ and it has been suggested that this is the result of it being incorporated into the virus nucleic acid to produce a non-infective species. 2,6-Diamino purine (2e) has been shown to be active against a variety of viruses, including polio virus, and organisms with virus-like properties.¹⁰



(7)



(8)

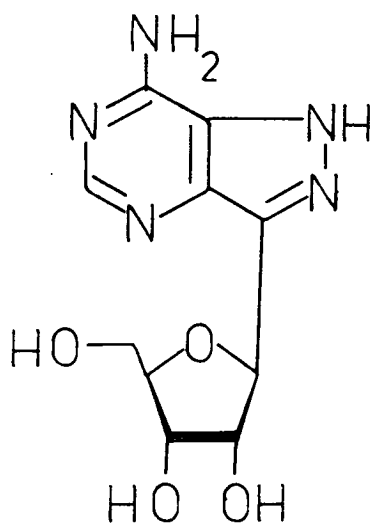
R

a; NHR

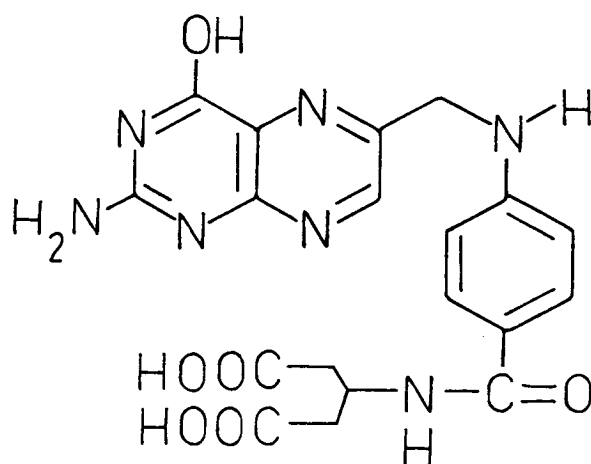
b; SR

c; OH

Scheme 3

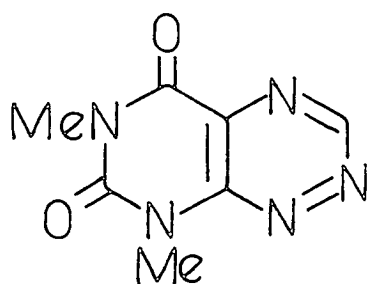


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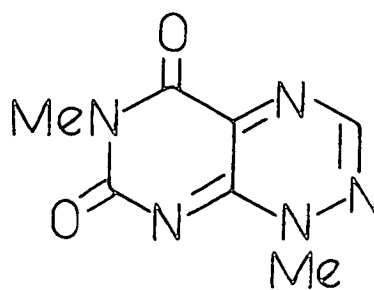


(10)

Scheme 4



(11)



(12)

Scheme 5

Various N-oxygenated purines (Scheme 2) have been demonstrated to have pronounced oncogenic (tumour-producing) properties, even in cases where the parent purine is inactive. The oncogenicity of N-oxygenated purines appears to depend on the position of the N-oxide substituent, as well as on the position of other substituents present. Thus, 3-hydroxyxanthine (3) and 7-hydroxyxanthine (4) (Scheme 2) both induce tumours^{11,12} whereas the parent purine, xanthine [(3) or (4); H for OH] shows no tumour-inducing activity.¹² As would be expected guanine shows no tumour-inducing activity,¹² in contrast with its oncogenic 7-hydroxy¹² and 3N-oxide derivatives.¹¹ 3-Hydroxy-8-azaxanthine (5) shows only weak oncogenicity,¹³ while Watson and Brown¹⁴ have demonstrated that 1-hydroxyxanthine (6) exhibits no marked oncogenic properties, although it does induce inflammations and granulomas at the site of injection. The oncogenic properties of N-oxygenated purines have been related to nucleophilic substitution reactions with cellular macromolecules.¹⁵⁻¹⁷

Pyrazolo[3,4-d]pyrimidines [Scheme 3; (7)] and pyrazolo[4,3-d]pyrimidines (8) are isosteric with purines and possess many purine-like properties. Several 6-alkylpyrazolo[3,4-d]pyrimidines have been reported to have coronary dilation properties,¹⁸ while 4-amino derivatives (7a) possess significant antitumour activity against adenocarcinoma and leukaemia in experimental animals.¹⁹ 4-Alkylthiopyrazolo[3,4-d]pyrimidines (7b) have been synthesised,²⁰ but, in marked contrast to mercaptopurines, they do not possess any biological activity. On the other hand 4-hydroxypyrazolo[3,4-d]pyrimidine (7c)²¹ has been shown to be effective against hyperuricemia and gout

in man. The antibiotic formycin [Scheme 4; (9)]²² contains the pyrazolo[4,3-d]pyrimidine ring system.

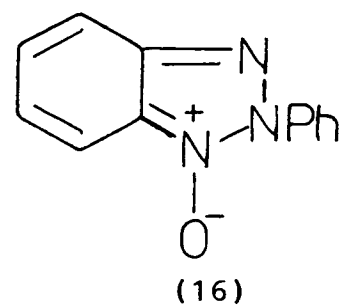
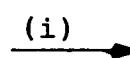
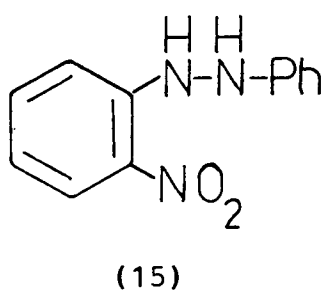
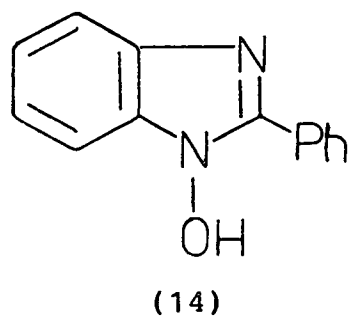
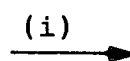
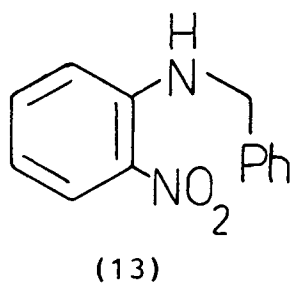
Pteridines also exhibit biological properties and have been isolated from natural sources, for example (Scheme 4) pteroylglutamic acid (vitamin B₉ or folic acid) (10).²³ The broad spectrum antibiotic fervenulin [Scheme 5; (11)]²⁴ possesses the unique pyrimido[5,4-e]-1,2,4-triazine nucleus, as does toxoflavin (12), which has antibiotic properties, but is also very toxic,²⁵ limiting its clinical usefulness.

The general synthetic strategy for potentially biologically active N-oxygenated purines, pteridines and related heterocycles adopted in the present study was based on the tendency of nitro and nitroso substituents to undergo base-catalysed cyclisation reactions to give N-oxygenated heterocycles in a single step. To this end the synthetic utility of suitably substituted nitroimidazoles, nitropyridazines and nitrosopyrazoles was investigated. As was that of those nitrobenzene derivatives appropriate as synthetic precursors of 'stretched-out' analogues of purines and pteridines, which are of current interest as dimensional probes for enzyme-coenzyme binding sites.²⁶

By way of background introduction, the discussion of the results obtained in these investigations is preceded by a review of the scope and mechanism of known cyclisation reactions of nitro and nitroso compounds leading to N-oxygenated purines, pteridines and related heterocycles.

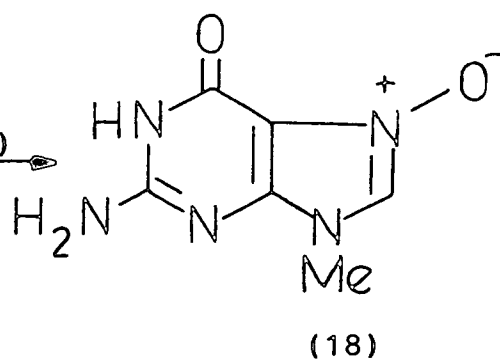
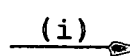
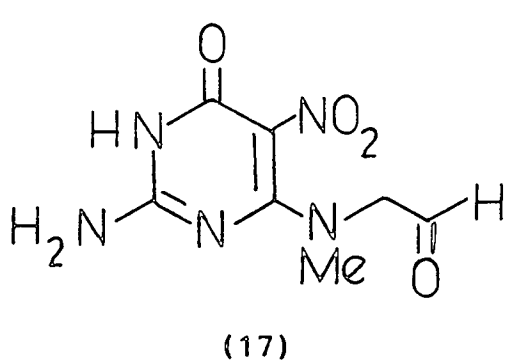
CHAPTER ONE

A Review of the Scope and Mechanism
of Cyclisation Reactions of Nitro and
Nitroso Compounds Leading to N-Oxygenated
Purines, Pteridines and Related Heterocycles



(i) OH^- .

Scheme 6



(i) $\text{NaOH}, \text{H}_2\text{O}.$

Scheme 7

A Review of the Scope and Mechanism of Cyclisation Reactions of Nitro and Nitroso Compounds leading to N-Oxygenated Purines, Pteridines and Related Heterocycles

a) N-Oxygenated Purines and Related Heterocycles

Purine N-oxides can be prepared by the direct oxidation of the parent system, but this method is only of value for certain 1- and 3-N-oxides and is limited in that any thio groups or halogen atoms present may be hydrolysed by the acidic peroxide conditions usually employed. Direct oxidation has not so far afforded a method for the synthesis of either purine 7-N- or purine 9-N-oxides.^{27,28} Therefore these N-oxygenated systems can only be obtained by synthetic routes. Peracid oxidation as a general method for N-oxygenated purine synthesis suffers from the disadvantage of lack of control over the site of N-oxidation. In contrast, cyclisation reactions of nitro or nitroso substrates provide potential, but little investigated, general methods for the synthesis of N-oxygenated purines of known orientation.

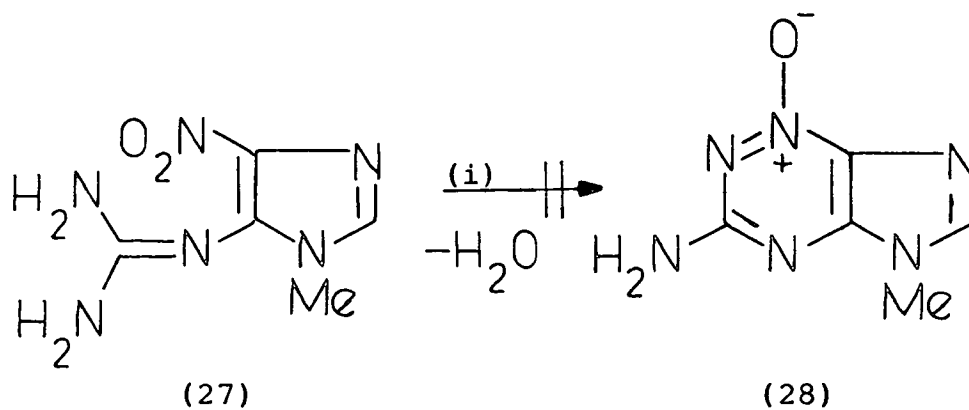
(i) Cyclisation Reactions of Nitro Compounds

The synthesis of a variety of N-oxygenated benz-fused heterocyclic systems can be effected by cyclisation, involving the intramolecular condensation of an aromatic nitro group with a suitable ortho side-chain. Such cyclisations have been reviewed in detail by Loudon and Tennant²⁹ and are exemplified (Scheme 6) by the base catalysed cyclisation of N-benzyl-2-nitroaniline (13) and 1-(2-nitrophenyl)-2-phenyl-

hydrazine (15) to 1-hydroxy-2-phenylbenzimidazole (14) and 2-phenylbenzo-1,2,3-triazole 1-N-oxide (16) respectively.

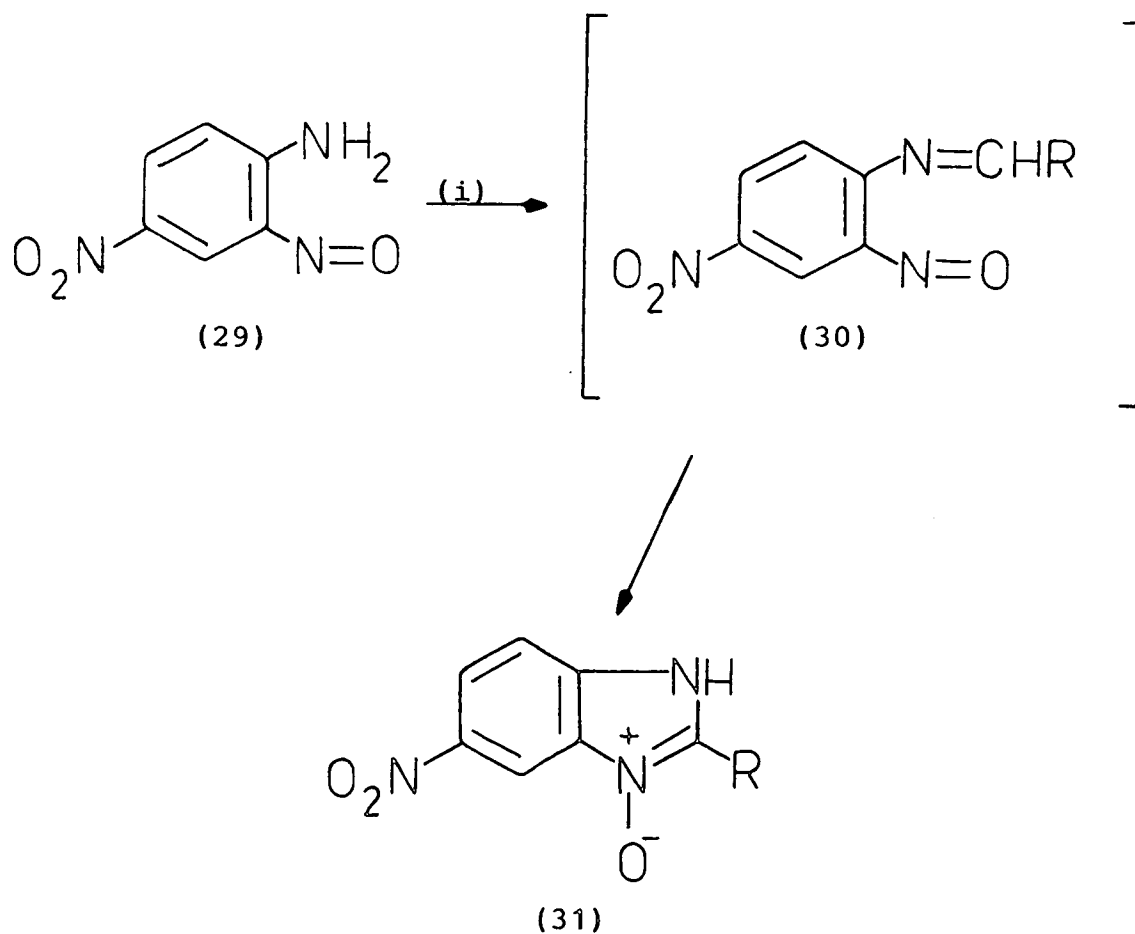
Perhaps the simplest example of a nitro-group ortho-side-chain interaction, to give a purine N-oxide, is that (Scheme 7) reported by Leigh et al.³⁰ who found that treatment of the 5-nitropyrimidin-4-ylaminoacetaldehyde (17) with cold aqueous sodium hydroxide affords 9-methylguanine 7-N-oxide (18) in quantitative yield. Maki, Izuta and Suzuki³¹ observed (Scheme 8) that 1,3-dimethyl-5-nitro-6-(benzylidene methylhydrazino)-uracil (19) undergoes photocyclisation to give the 8-azapurine 7-N-oxide (23) in low yield (35%), together with the pyrazolo-pyrimidinedione (21). The formation of the N-oxide (23) appears to be initiated by cycloaddition of the nitro-group to the photo-excited imine (C=N) bond of the hydrazone side-chain, to give the intermediate (20). This can then collapse, with loss of benzaldehyde, to give the strained oxadiaziridine intermediate (22), isomerisation of which accounts for the formation of the azapurine N-oxide (23). The pyrazolo-pyrimidine-dione product (21) presumably arises by a photocyclisation process involving the elimination of the nitro substituent in the hydrazinouracil (19). In an alternative approach to 8-azapurine 7-N-oxides (Scheme 9) Defusio and Strauss³² have shown that 4-chloro-5-nitropyrimidines such as (24) react with phenylhydrazine to give the corresponding 4-hydrazino-5-nitropyrimidines [e.g. (25)] which undergo acid-catalysed cyclisation to the corresponding azapurine N-oxides [e.g. (26)].

Attempts (Scheme 10) have been made to carry out the base-catalysed cyclisation of nitroimidazolylguanidines such



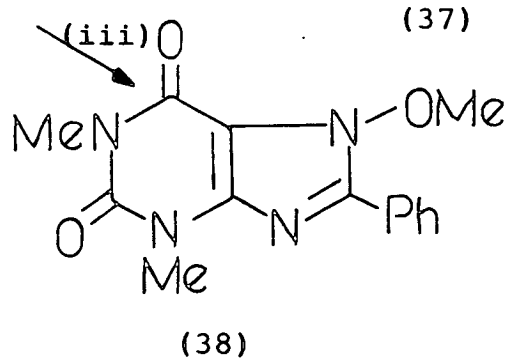
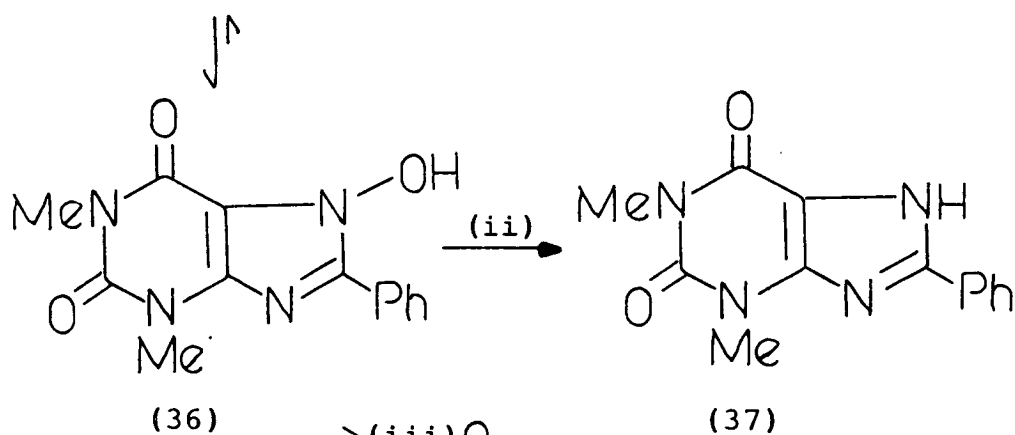
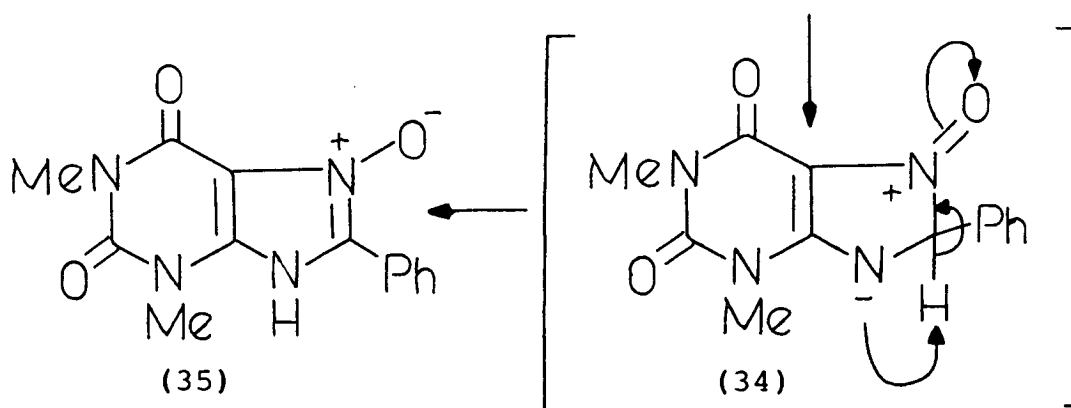
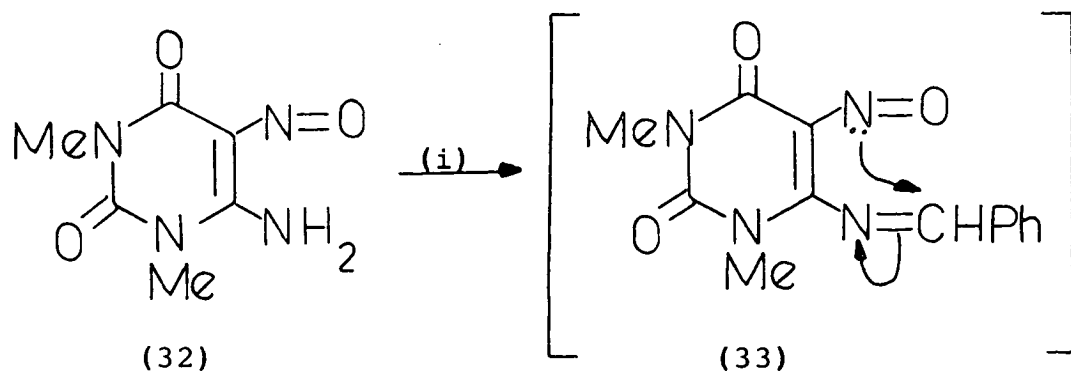
(i) Base .

Scheme 10



(i) RCHO .

Scheme 11



(i) PhCH=O .

(ii) $[\text{H}]$.

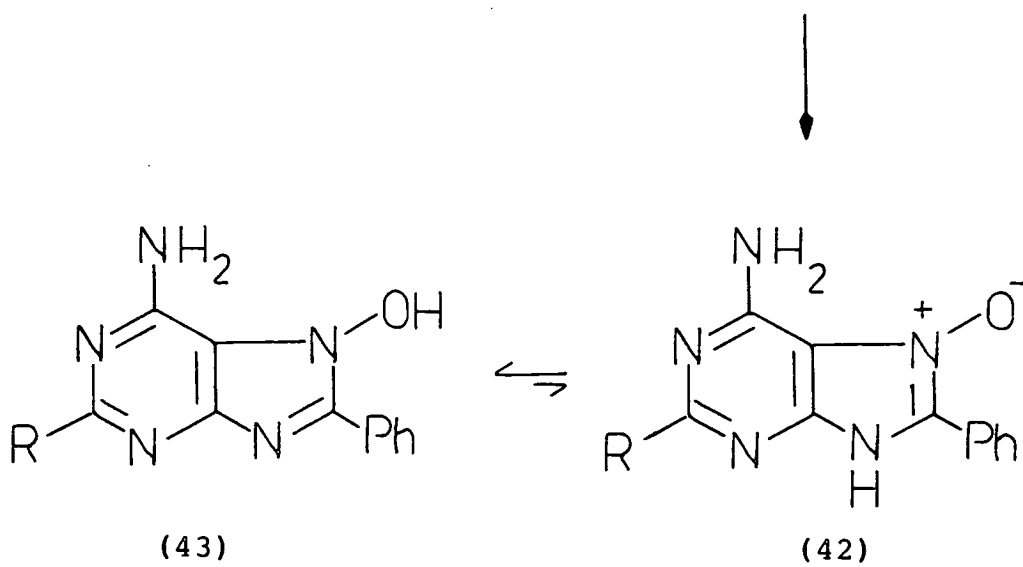
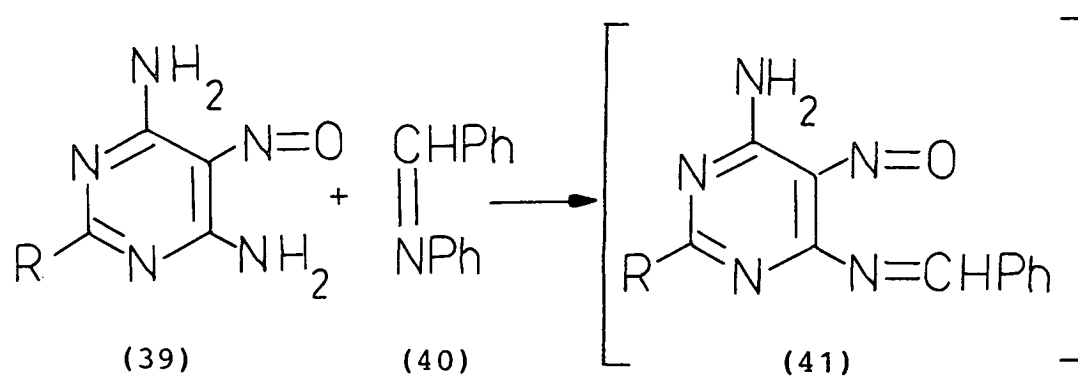
(iii) Me_2SO_4 , NaOH .

as (27) to afford 1-azapurine 1-N-oxides (28) without success.³³ The treatment of the 5-guanidino-4-nitroimidazole (27) with warm aqueous alkali, ethanolic sodium ethoxide or anhydrous sodium acetate in glacial acetic acid resulted in the complete degradation of the molecule and attempted cyclisation using sodium amide in ammonia or diethylene glycol dimethylether left the imidazole system (27) unchanged.

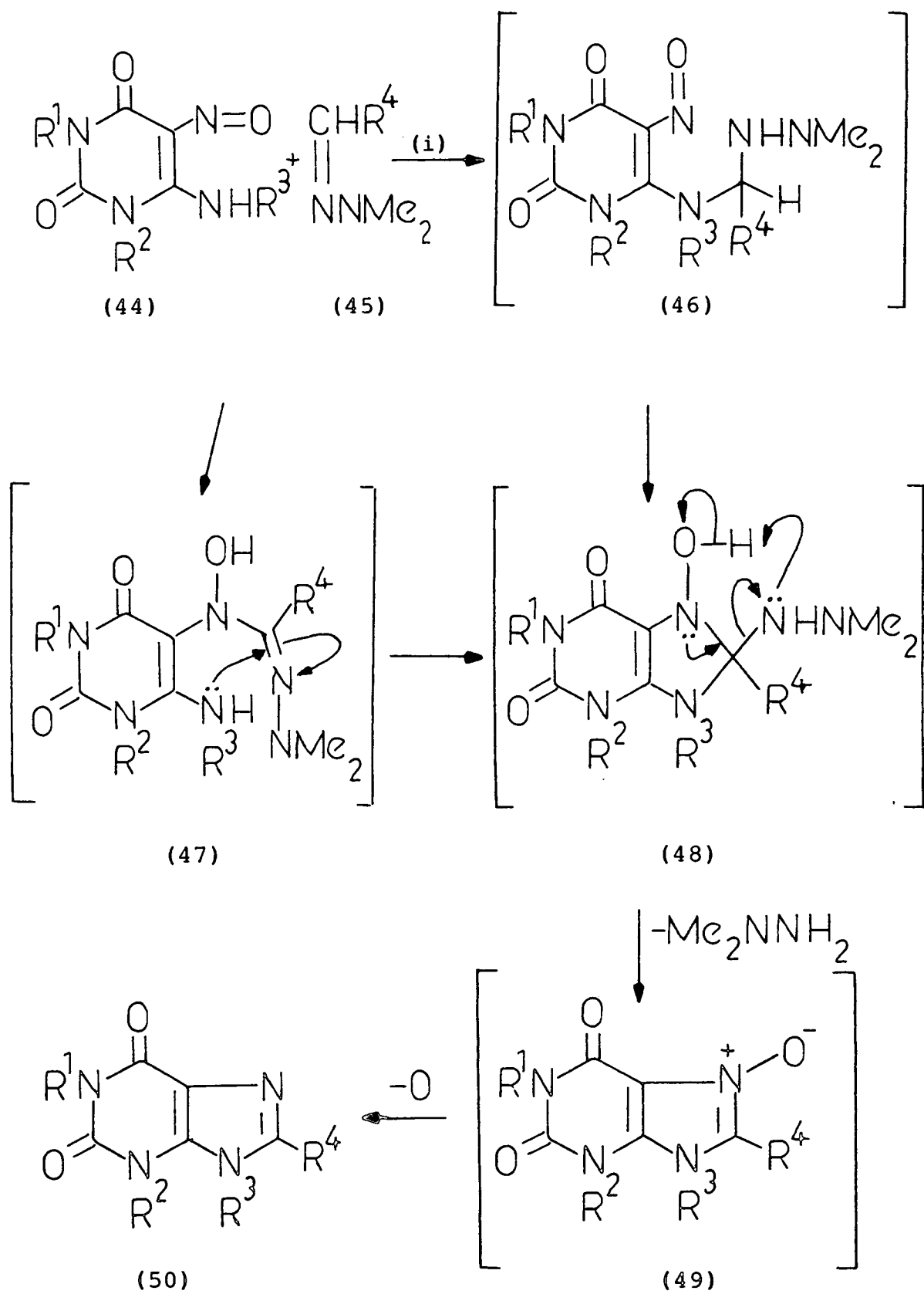
(ii) Cyclisation Reactions of Nitroso Compounds

The synthesis of N-oxygenated benz-fused heterocycles from ortho-substituted nitrosobenzenes has been reviewed by Katritzky and Lagowski²⁸ and is exemplified (Scheme 11) by the spontaneous cyclisation of the intermediate anils (30), produced by the condensation of ortho-nitrosoanilines [e.g. (29)] with aldehydes, to give benzimidazole 1-N-oxides (31).

Perhaps the simplest example of an N-oxygenated purine synthesis from a nitroso derivative is that described by Taylor and Garcia³⁴ (Scheme 12) who showed that 4-amino-1,3-dimethyl-5-nitrosouracil (32) reacts with benzaldehyde in dimethylformamide to afford a mixture of the N-hydroxypurine (36) and the parent theophylline derivative (37). The structure of the 7-hydroxypurine (36) was confirmed by its methylation to give the O-methyl derivative (38) and its role as an intermediate in the co-formation of the theophylline (37) was verified by the formation of the latter when the N-hydroxypurine (36) was heated in dimethylformamide. These authors also demonstrated³⁴ that cyclisation in the presence of a reducing agent such as formic acid affords only the desired synthetic target, the theophylline derivative (37),



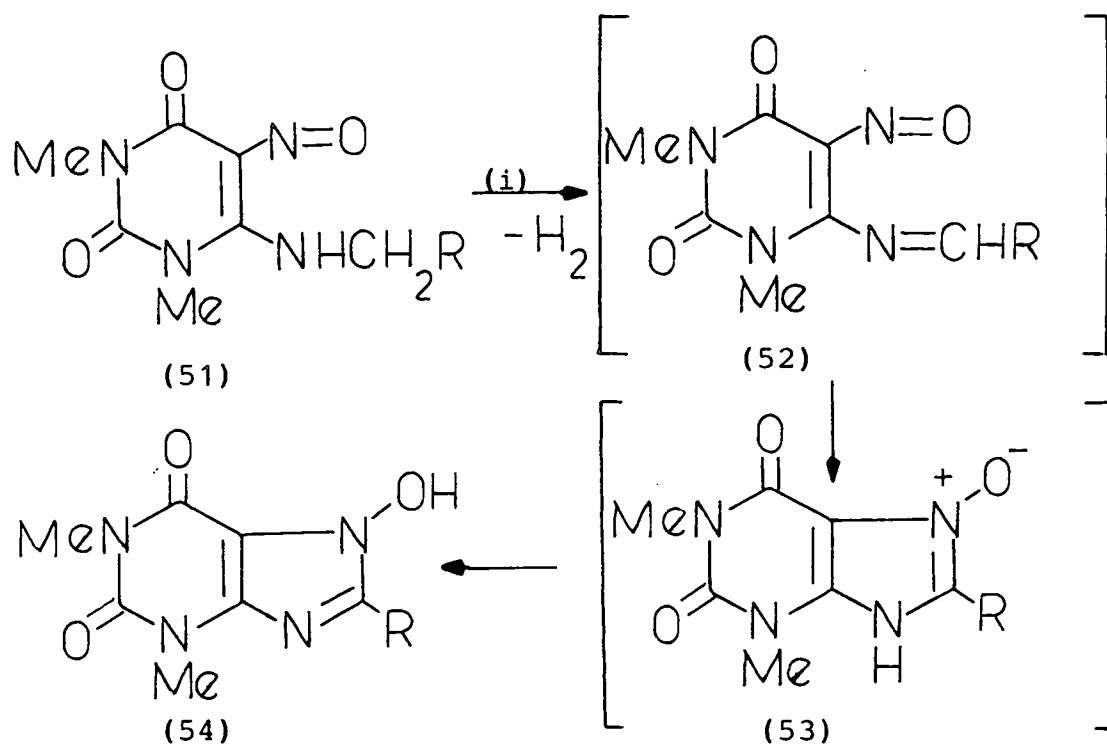
Scheme 13



(i) dimethylformamide, heat.

and none of the N-hydroxypurine (36). Moreover, use of the formic acid-dimethylformamide conditions with a variety of aldehydes provided a general route to 8-substituted theophyllines. In closely related reactions (Scheme 13) 4,6-diamino-5-nitrosopyrimidines (39) condense with benzyldene-aniline (40) to yield 7-hydroxypurines (43) possibly via the corresponding imine intermediates (41).³⁵ The postulated mechanism for the formation of the 7-hydroxypurines (43) involves the initial formation of the intermediate imines (41), these spontaneously cyclise to the N-oxides (42) which exist in the preferred 7-hydroxy tautomer structures (43).

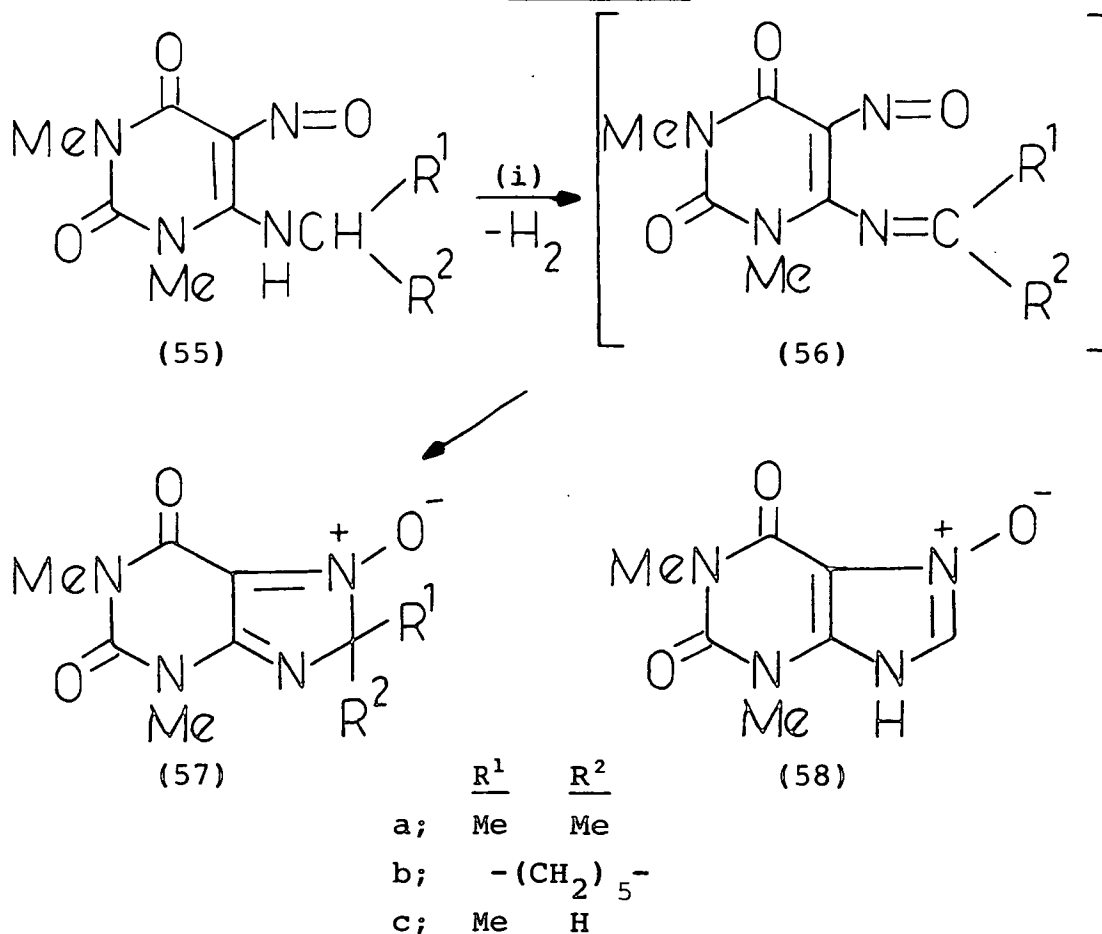
Purine N-oxides and N-hydroxypurines have been reported as possible intermediates in several synthetic routes to purines. For example (Scheme 14), Yoneda and Nagamatsu³⁶ described the synthesis of 9-substituted xanthines (50) from 6-amino-5-nitrosouracils (44) by reaction with the 1,1-dimethylhydrazones of a wide variety of aldehydes. One possible mechanism for the formation of the purines (50) in such reactions involves the formation of the intermediate nitroso derivatives (46), which can spontaneously cyclise to the N-hydroxypurine intermediates (48). Subsequent elimination of 1,1-dimethylhydrazine from the latter compounds would then give the N-oxides (49). Deoxygenation of these intermediates then affords the 9-substituted xanthines (50). However, the mechanism postulated by Yoneda and Nagamatsu³⁶ involves the initial nucleophilic attack on the nitroso group in the pyrimidines (44) by the electron rich α -carbon centre in the hydrazones (45) to give hydroxylamine intermediates (47), which can then cyclise, eliminate 1,1-dimethylhydrazine and undergo



(i) isoamyl nitrite.

(R=Me, Ph, Et, CH₂OH)

Scheme 15

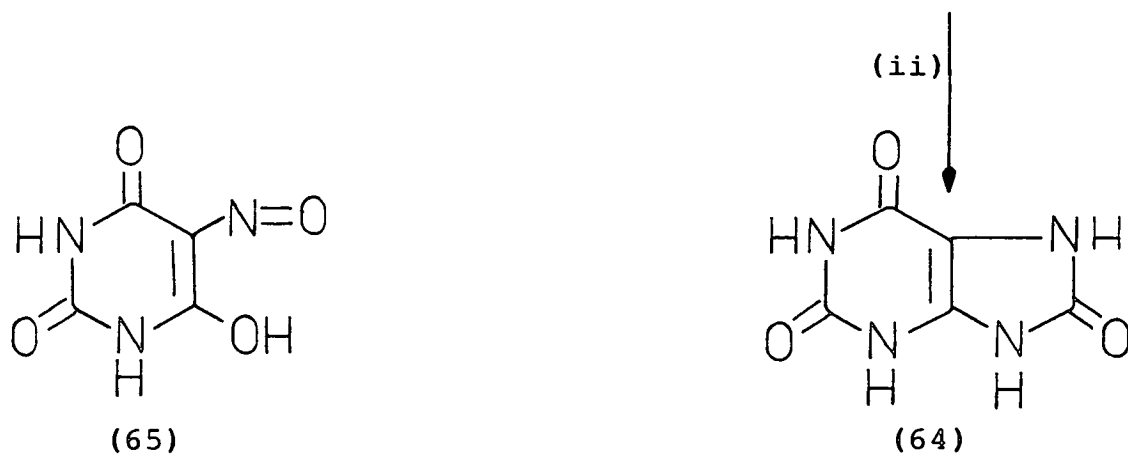
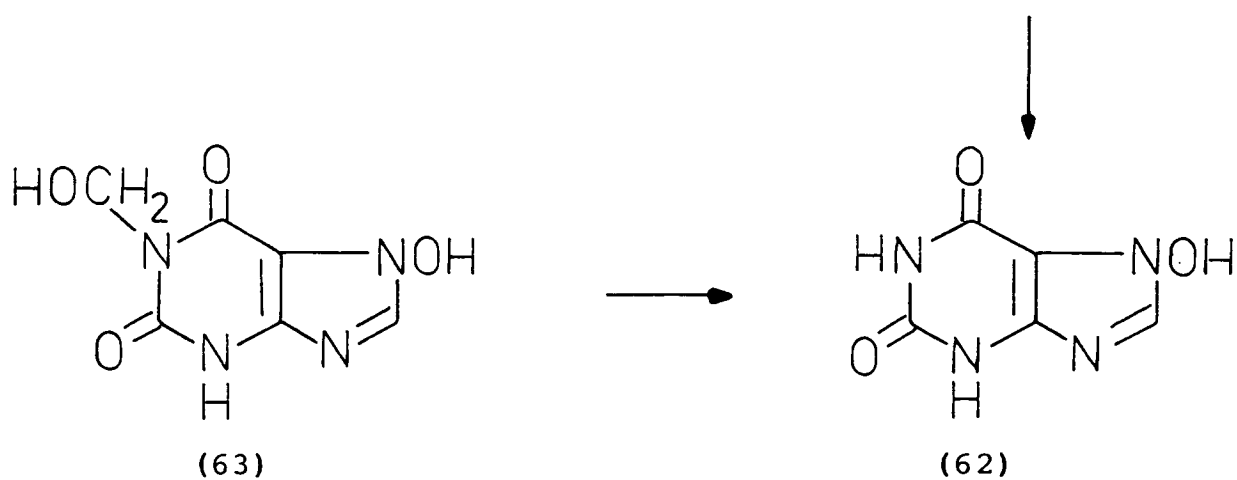
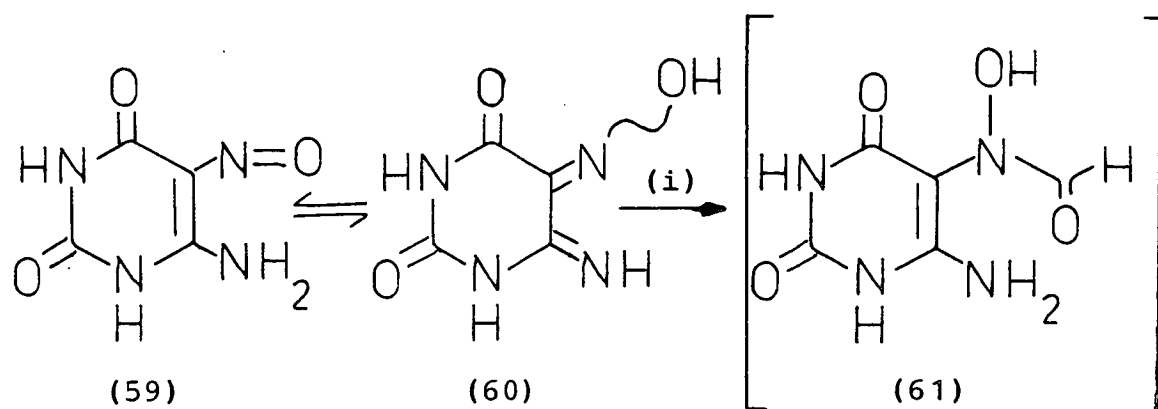


(i) isopropyl nitrite or isopentyl nitrite.

Scheme 16

deoxygenation to give the 9-substituted xanthines (50) as before.

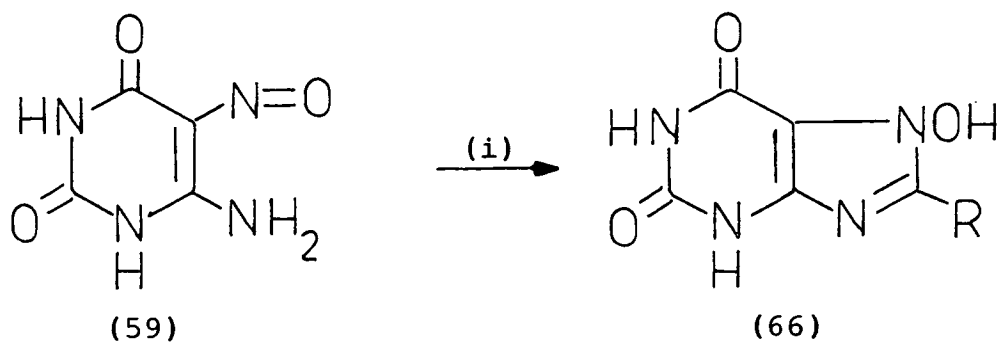
Goldner, Dietz and Carstens have synthesised (Scheme 15) a variety of 7-hydroxyxanthines (54) by oxidative cyclisation of 4-alkylamino-5-nitrosouracils (51) using isoamyl nitrite.^{37,38} It has been suggested³⁷ that these cyclisations occur by dehydrogenation of the alkylamines (51) to the corresponding imines (52), which then cyclise spontaneously to the appropriate N-oxides (53) rearrangement of which yields the 7-hydroxytheophyllines (54). A variant³⁹ of this type of cyclisation (Scheme 16) allows the synthesis of the corresponding 8,8-disubstituted purine 7-N-oxides (57) from 4-sec-alkylamino-5-nitrosopyrimidines (55). Thus, treatment of the nitrosopyrimidines (55a) and (55b) with isopropyl nitrite or isopentyl nitrite results in smooth cyclisation to 1,3,8,8-tetramethylxanthine 7-N-oxide (57a) and 1,3-dimethyl-8,8-pentamethylenexanthine 7-N-oxide (57b) respectively, presumably via the imine intermediates (56), in moderate yields. The synthesis of 1,3,8,8-tetramethylxanthine 7-N-oxide (57a) has also been achieved by oxidative cyclisation of 1,3-dimethyl-4-isopropylamino-5-nitrosouracil (55a) using aqueous acidic potassium dichromate.³⁸ Other oxidising agents, such as aqueous nitric acid and aqueous acidic potassium permanganate have also been used to effect such cyclisations, but these reagents can result in the oxidative removal of the 8-alkyl substituent. Thus the oxidative cyclisation of the ethylamino-nitrosopyrimidine derivative (55c) using acidified potassium permanganate affords 1,3-dimethylxanthine 7-N-oxide (58) (Scheme 16).⁴⁰



(i) HCH=O , H_2O , 100° .

(ii) H_2O , heat.

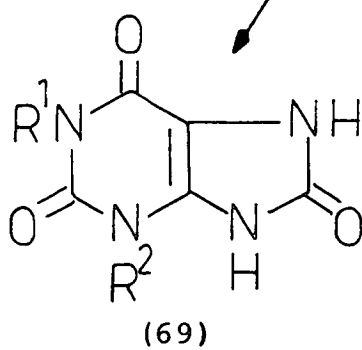
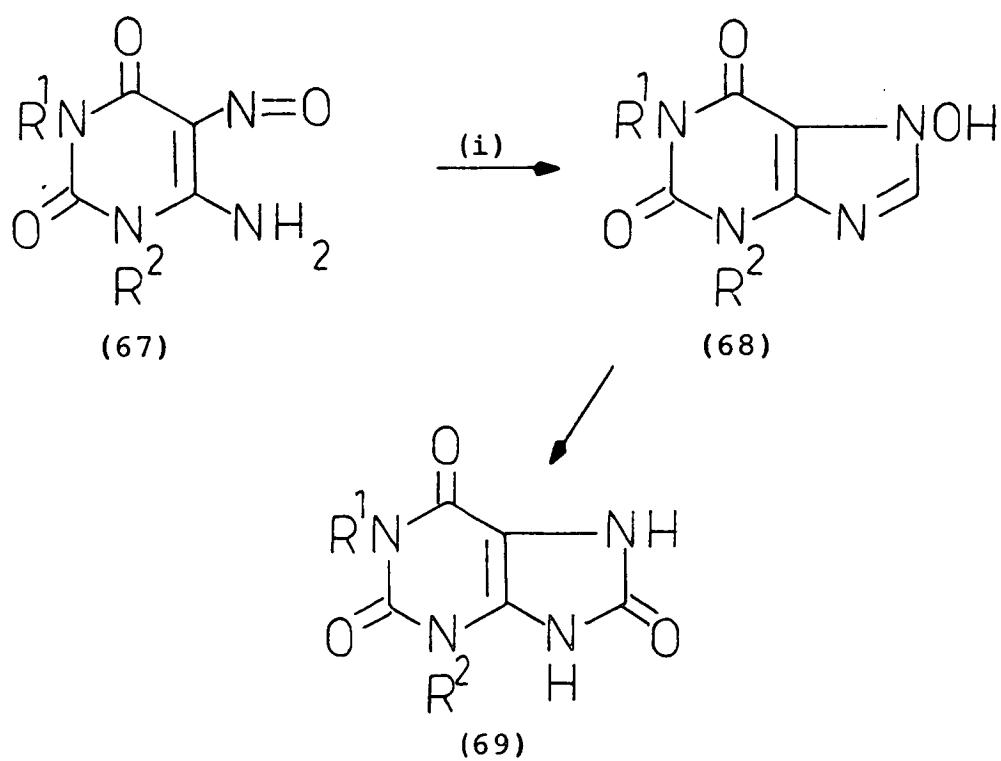
Scheme 17



(i) $RCH=O$.

($R=C_5H_{11}$ or C_6H_{13})

Scheme 18

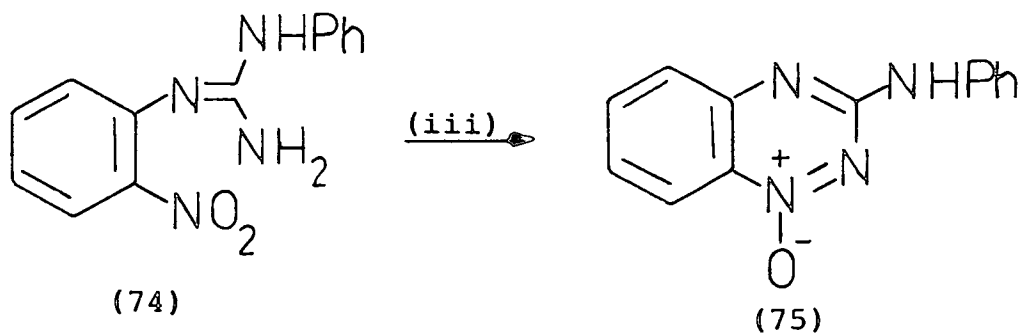
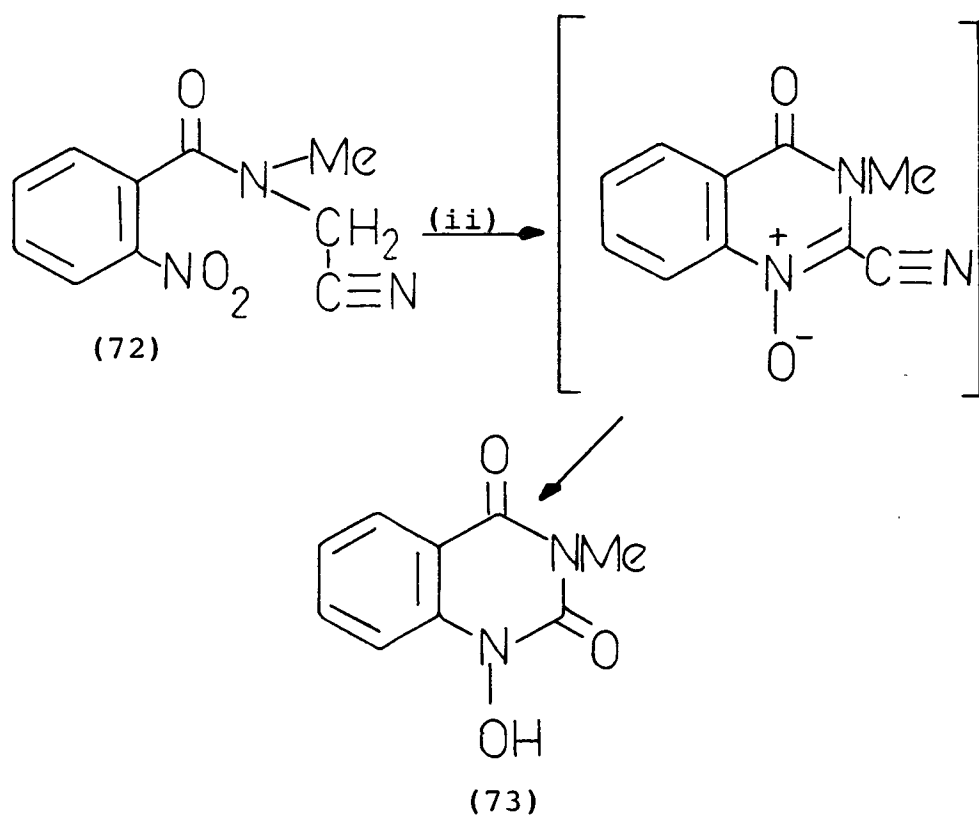
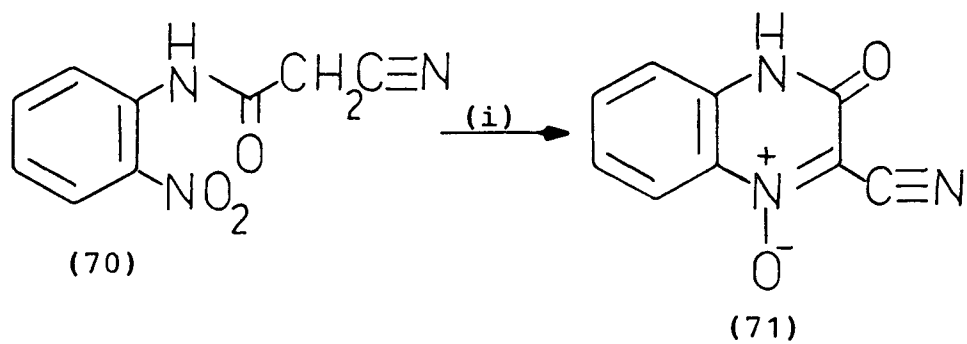


	<u>R¹</u>	<u>R²</u>
a;	Me	H
b;	H	Me

(i) $HCH=O$, H_2O .

Scheme 19

The synthesis of N(1)- and N(3)-unsubstituted 7-hydroxy-xanthines has been investigated by Zvilichovsky and Brown,⁴¹ who found that methods based on oxidative cyclisations of the type already discussed failed for substrates unsubstituted at the N(1)- and N(3)-positions. Therefore, they developed an alternative route to such N-oxygenated purines, illustrated (Scheme 17) by the reaction of 6-amino-5-nitrosouracil (59) with aqueous formaldehyde to give a readily separated mixture of 7-hydroxyxanthine (62), its N-hydroxymethyl derivative (63) and uric acid (64). The success of this reaction was shown to be both pH and time dependent. At pH <2.5 hydrolysis occurs to afford 5-nitrosobarbituric acid (65) as the sole product, while at pH >3.5 no reaction was observed. The formation of uric acid (64) is believed⁴¹ to result from rearrangement of 7-hydroxyxanthine (62), so the longer the reaction time the greater the yield of uric acid (64) obtained. It was also demonstrated⁴¹ that heating an aqueous solution of 1-hydroxymethyl-7-hydroxyxanthine (63) affords 7-hydroxyxanthine (62) and it is proposed⁴¹ that the initial hydroxymethylation at the N(1)- and N(3)-positions of the starting nitrosopyrimidine (59) may be a requirement for successful cyclisation. It was also proposed that the intermediate (61) is formed by the reaction of formaldehyde with the oxime tautomer (60) of the aminouracil (59) and not the nitrosouracil (59) itself (Scheme 17). An extension of the Zvilichovsky-Brown 7-hydroxypurine synthesis involves the reaction (Scheme 18) of 4-amino-5-nitrosouracil (59) with aliphatic aldehydes in dimethylsulphoxide at controlled temperatures to afford 8-alkyl-7-hydroxyxanthines (66) in good yield. The improved yields in these cyclisations



(i) 4% NaOH (aq)-pyridine, 24°, 1 h.

(ii) NaOEt-EtOH, reflux, 1 hr or 10% NaOH (aq)-EtOH, reflux.

(iii) NaOH, H₂O, reflux.

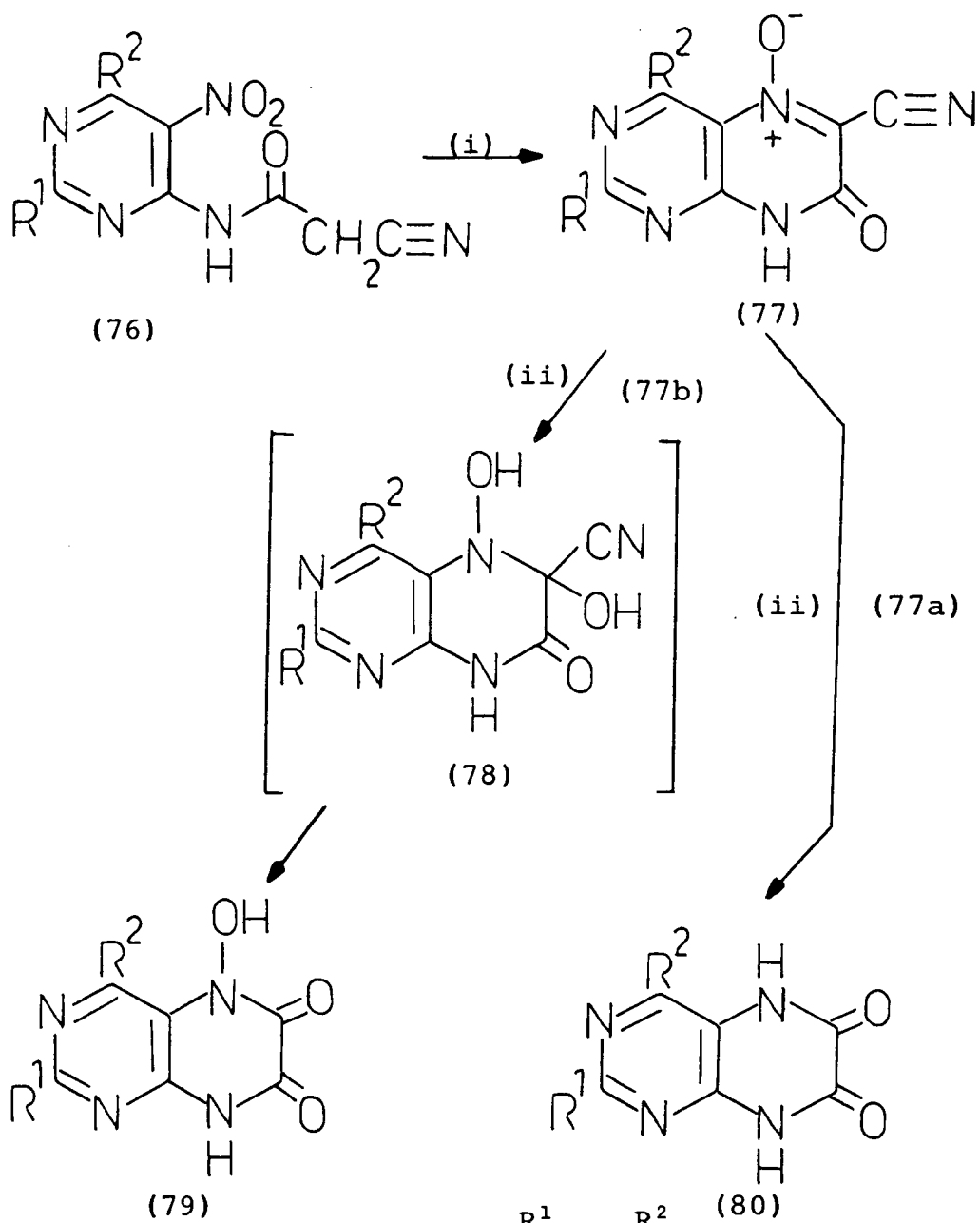
are presumably due to inhibition of the rearrangement to a corresponding uric acid derivative.

The first synthesis of monosubstituted 7-hydroxyxanthines was described by Zvilichovsky and Feingers⁴² who reacted (Scheme 19) 4-amino-1-methyl-5-nitrosouracil (67a) with formaldehyde in dimethylsulphoxide at 117-119° to obtain 7-hydroxy-1-methylxanthine (68a) in 40% yield. However, the use of higher temperatures in this reaction resulted in the formation of the uric acid (69a), presumably by rearrangement of the initially formed 7-hydroxyxanthine (68a). The attempted synthesis of 7-hydroxy-3-methylxanthine (68b) was unsuccessful, the only product isolated being 3-methyluric acid (69b), which is considered to arise from (68b) via an N-hydroxymethyl intermediate.

b) N-Oxygenated Pteridines and Related Compounds

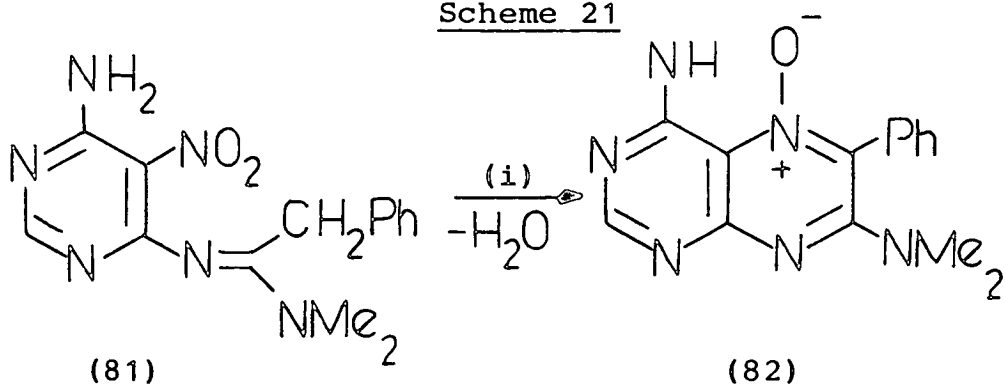
(i) Cyclisation Reactions of Nitro Compounds

The synthesis of quinoxaline, quinazoline and benzo-1,2,4-triazine N-oxides by base catalysed aldol type condensations of substituents containing an activated methylene group ortho to a nitro group, have been reviewed by Preston and Tennant.⁴³ These cyclisations have been effected by a variety of bases and often in high yield. For example, (Scheme 20) treating the α-cyano-ortho-nitroacetanilide (70) with a mixture of sodium hydroxide and pyridine at room temperature gives a good yield of the 2-cyanoquinoxalin-3(4H)-one 1-N-oxide (71). Correspondingly, the N-hydroxyquinazoline (73) can be obtained in excellent yield by treating the amide (72)



(i) NaOH, H₂O, 40°. a; NMe₂ Me
 (ii) NaOH, H₂O, reflux. b; NMe₂ H

Scheme 21



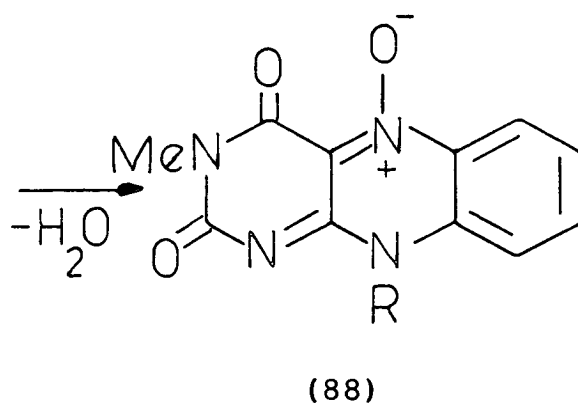
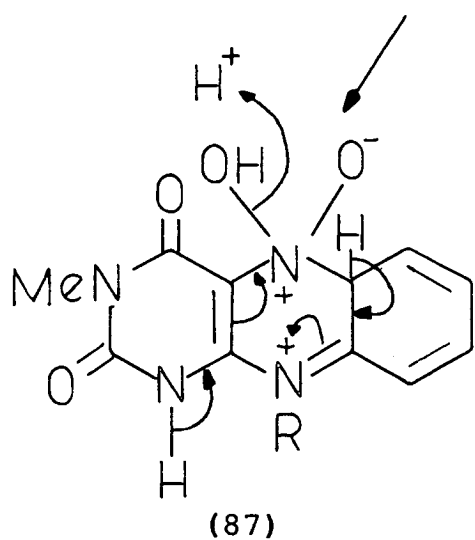
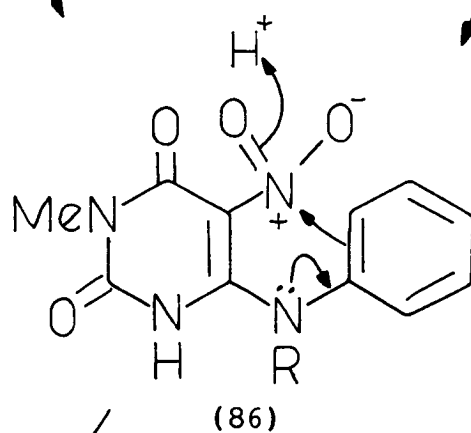
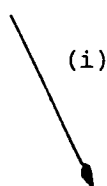
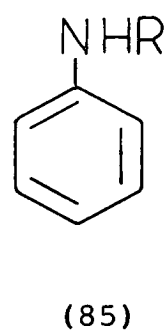
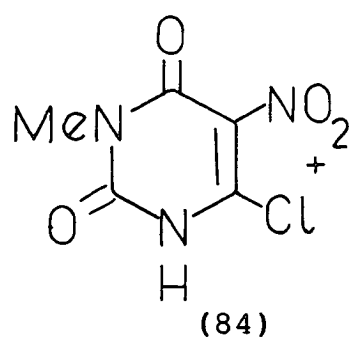
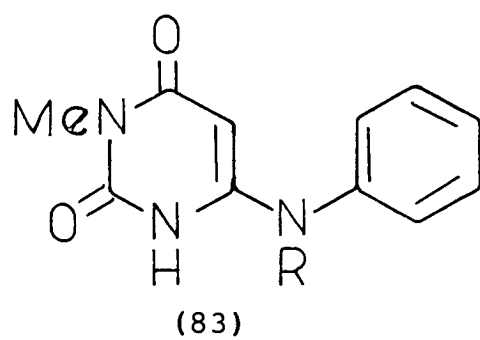
(i) NaOEt.

Scheme 22

with sodium ethoxide or ethanolic sodium hydroxide; the corresponding 2-cyanoquinazolinone N-oxide being a plausible intermediate in this transformation. The N-(2-nitrophenyl)-guanidine derivative (74) undergoes base catalysed cyclisation to the benzo-1,2,4-triazine N-oxide (75) in quantitative yield on treatment with aqueous sodium hydroxide.

Perhaps the simplest example of a synthesis of N-oxygenated pteridines involving nitro-group ortho side-chain interaction is that (Scheme 21) described by Yacomini and Tennant,⁴⁴ who showed that treatment of 4-(2-cyanoacetamido)-5-nitropyrimidines (76) with dilute sodium hydroxide at 40° gave the 2-dialkylaminopteridin-7(8H)-one 5-N-oxides (77) in good yield. When these cyclisations were carried out under reflux, the products were the corresponding N-hydroxypteridinediones (79), together with the pteridinediones (80). The formation of the hydroxamic acid (79b) was shown to arise by the hydrolysis of the corresponding N-oxide (77b) via the proposed intermediate (78b) by taking the N-oxide (77b), isolated at 40°, and heating it under reflux in sodium hydroxide. Correspondingly, heating the 4-methylpteridine 5-N-oxide (77a) afforded the pteridine-dione (80a) and not the hydroxamic acid (79a). The hydroxamic acid (79b) was shown to be stable to thermal deoxygenation under the reaction conditions used and it is suggested that the mechanism for the formation of the pteridinedione (80a) does not involve the in situ reduction of the cyclic hydroxamic acid (79a).

Another example (Scheme 22) of base-catalysed nitro-group ortho-side-chain interaction leading to pteridine 5-N-oxides is provided by the sodium ethoxide catalysed conversion of



R

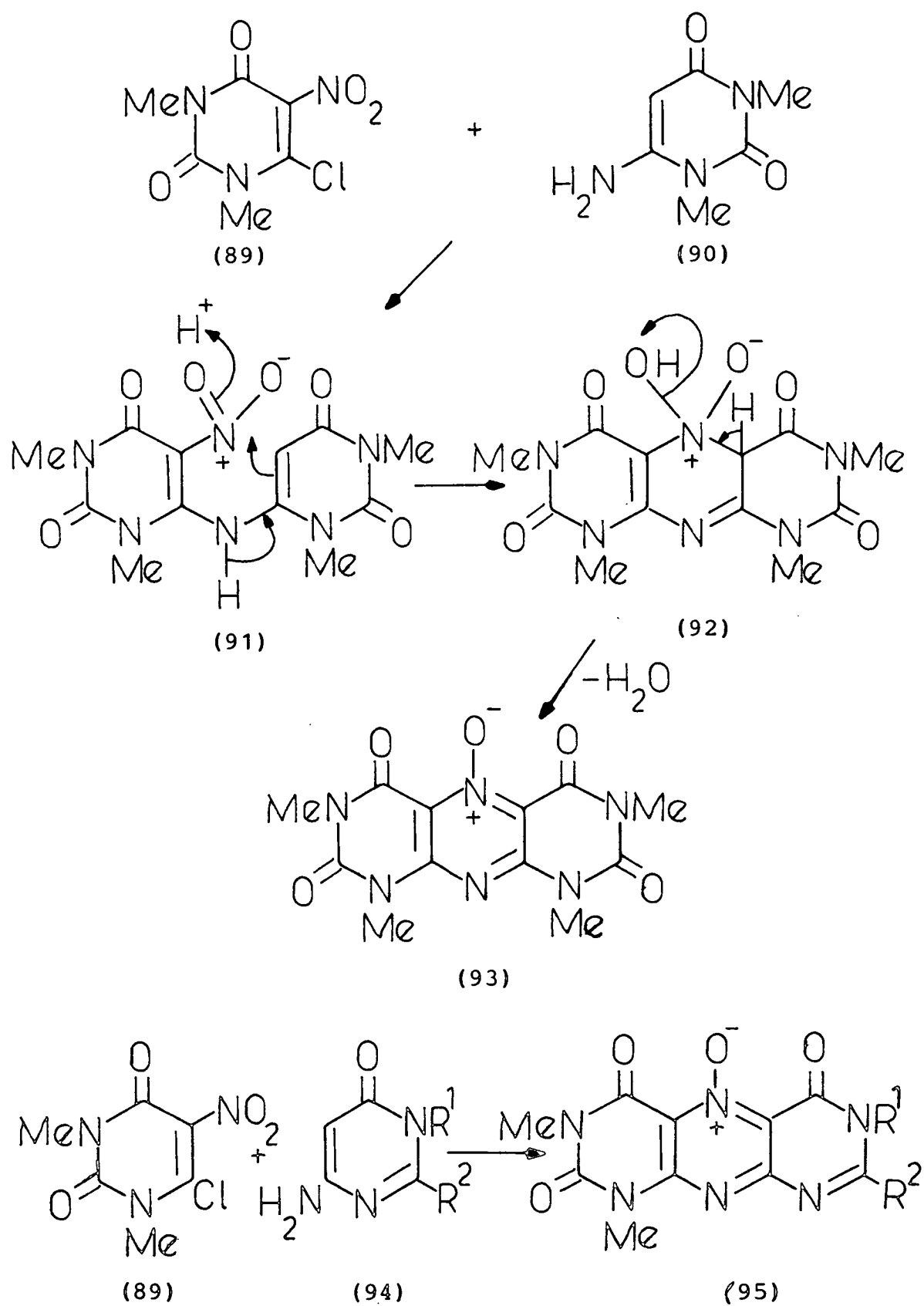
a; Me

b; Et

c; Buⁿ

(i) NaNO₂, AcOH.

Scheme 23

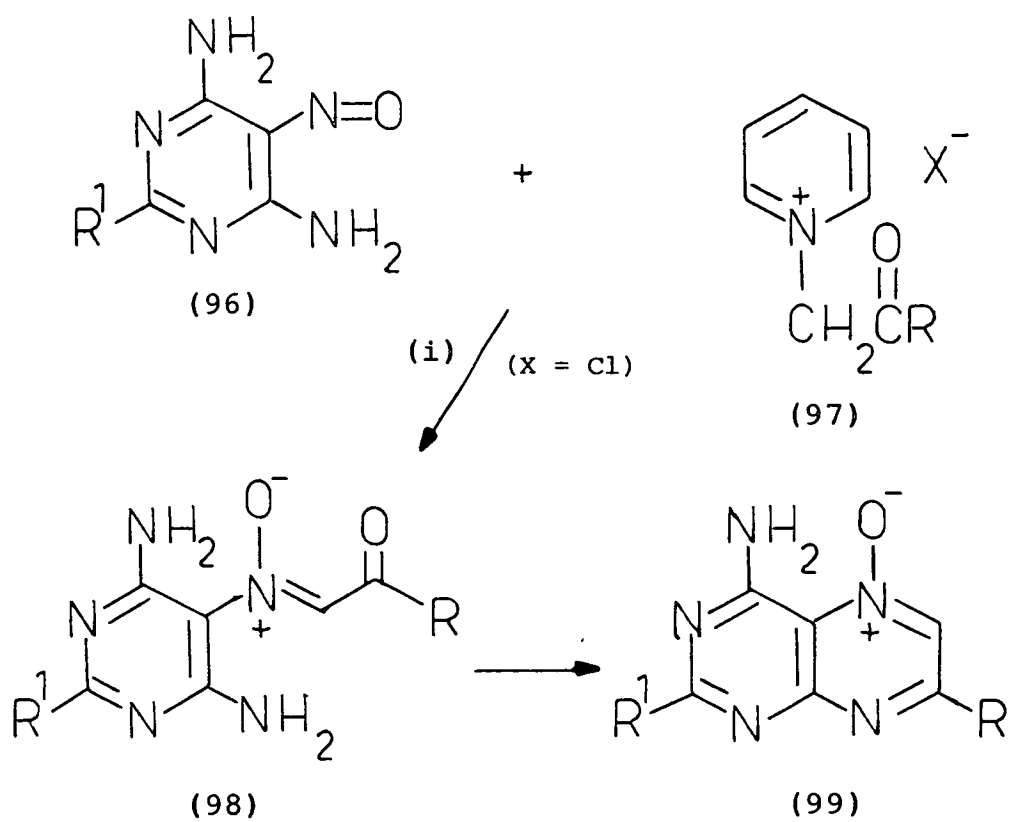


Scheme 24

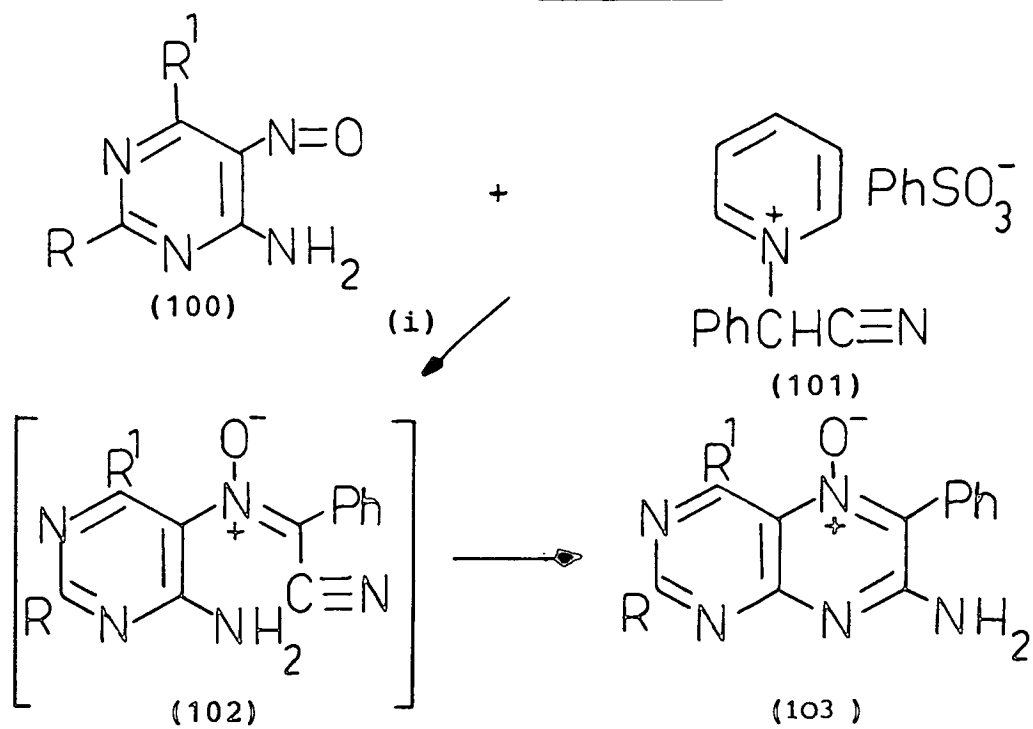
amidino-nitropyrimidines (81) into 1,6-diaminopteridine 8-N-oxides (82).⁴⁵

Isoalloxazine 5-N-oxides (88) can be synthesised (Scheme 23) in reasonable yields by the spontaneous cyclisation of N-alkylanilino-nitrouracils (86) produced in situ by nitration of the corresponding N-alkylanilinouracils (83).⁴⁶ In accordance with the intermediacy of the anilino-nitrouracils (86) in these cyclisations, the latter compounds can be pre-formed (Scheme 23) from chloro-nitrouracils (84) and aniline derivatives (85) and undergo cyclisation to the corresponding isoalloxazine 5-N-oxides (88) on treatment with excess concentrated sulphuric acid.^{47,48}

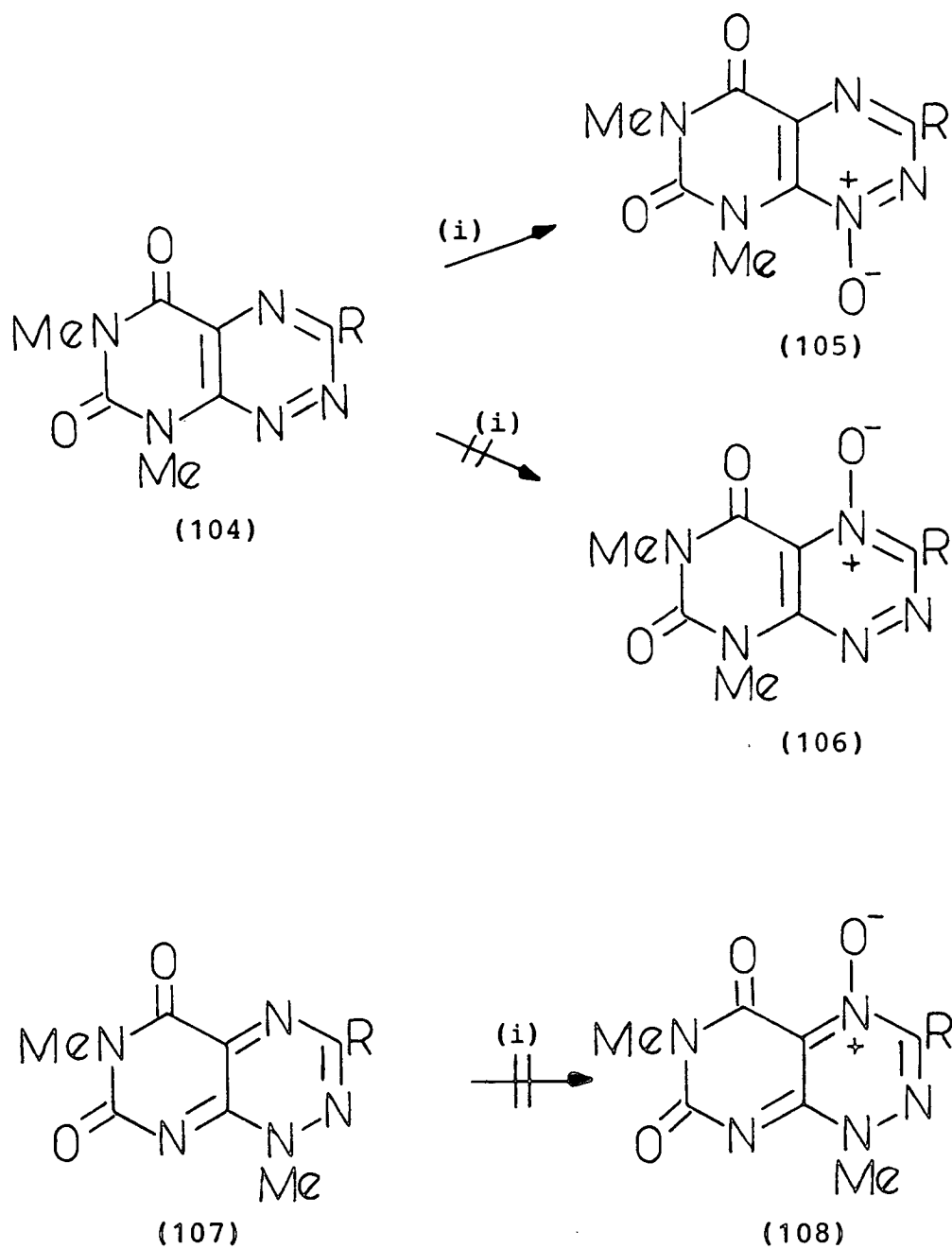
Taylor, Maki and Sako⁴⁹ demonstrated the synthesis (Scheme 24) of pyrimidopteridine 10-N-oxides (93) and (95) by a thermal nitro group interaction, and propose that hydrolysis of these tricyclic N-oxides could provide a route to pteridine N-oxides. Thus, heating 1,3-dimethyl-5-nitro-6-chlorouracil (89) with 6-aminouracils (90) or 6-aminopyrimidinones (94) under reflux in dimethylformamide for 0.5 to 1 hour afforded the pyrimidopteridine 10-N-oxides (93) and (95) respectively, in moderate to good yields. The reaction time is important as prolonged heating of the N-oxide results in contamination by the deoxygenated product. The mechanism (Scheme 24) proposed⁴⁹ for these cyclisation reactions involves the nucleophilic displacement of the chlorine substituent in the uracil (89) to give an intermediate (91) which cyclises via the nitro-group as shown to give the observed pyrimidopteridine N-oxides (93) and (95).



Scheme 25



Scheme 26



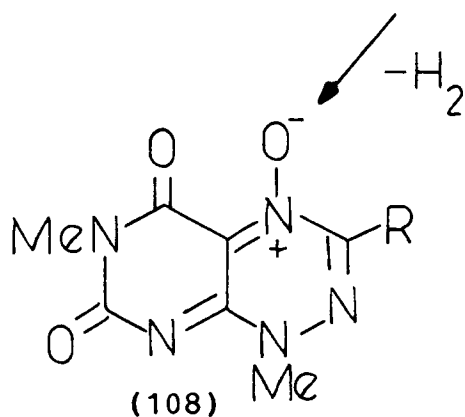
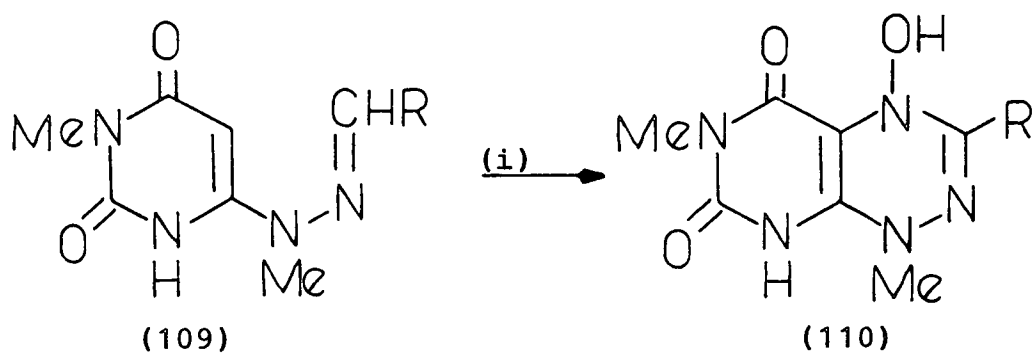
R

a; H

b; Ph

(i) peracid.

Scheme 27



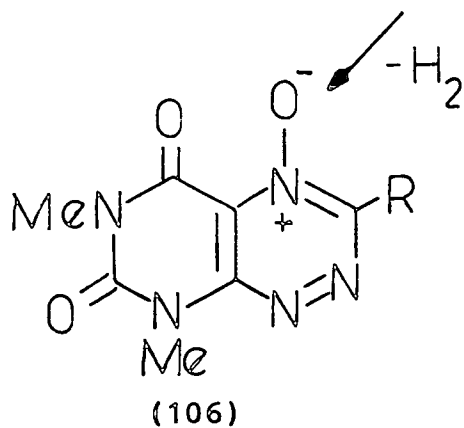
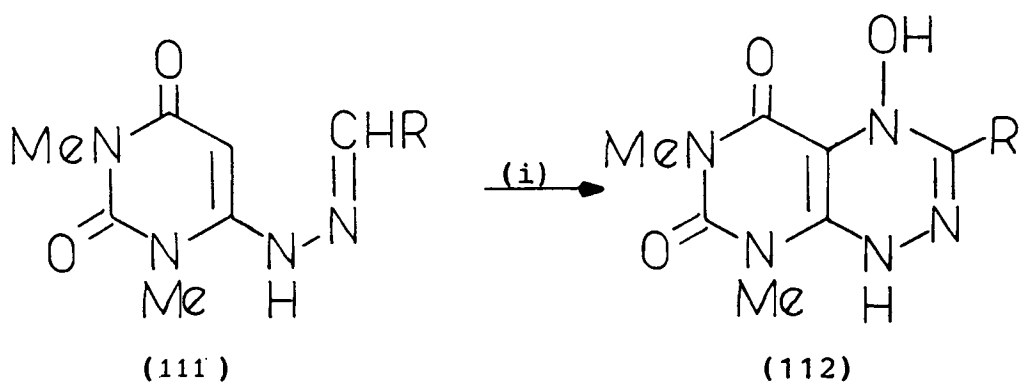
R

a; H

b; Ph

(i) NaNO_2 , diethylazodicarboxylate or NaNO_2 , diethylazodiformate.

Scheme 28



R

a; H

b; Ph

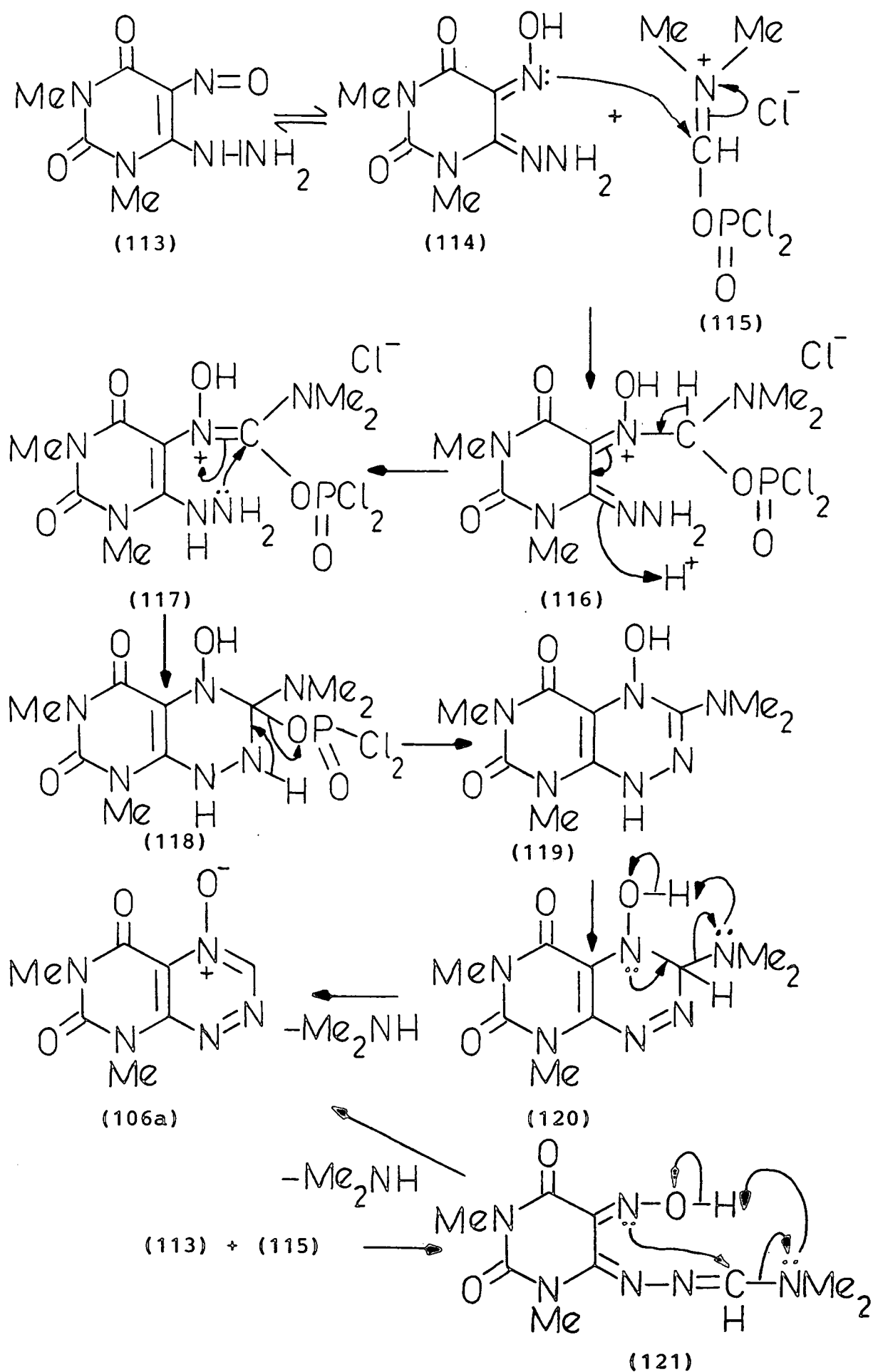
(i) NaNO_2 , diethylazodicarboxylate or NaNO_2 , diethylazodiformate

Scheme 29

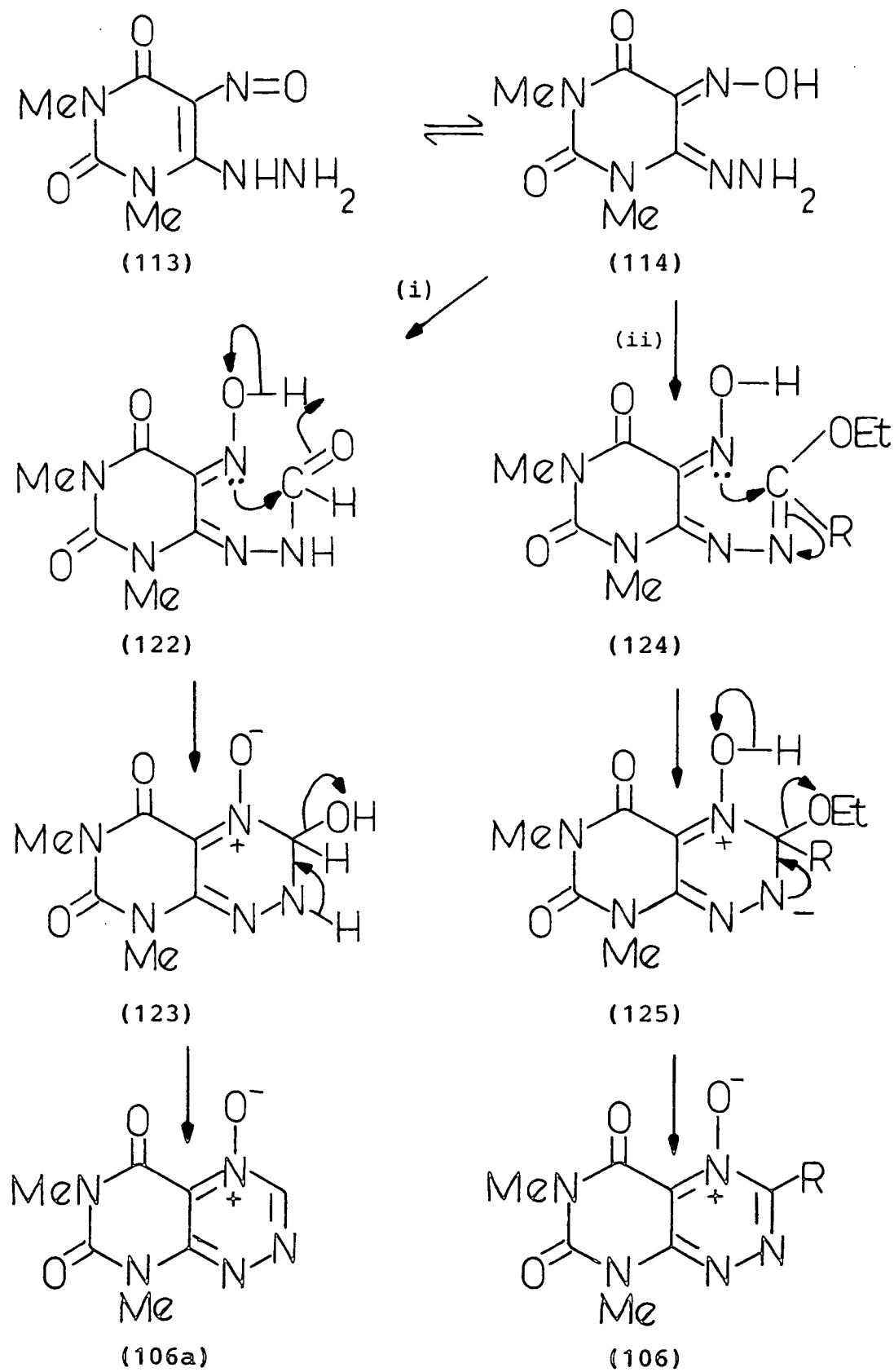
(ii) Cyclisation Reactions of Nitroso Compounds

Cyclisation of amino-nitrosopyrimidines to N-oxygenated pteridines was first reported by Pachter, Nemeth and Villani⁵⁰ (Scheme 25). These workers showed that 4-amino-5-nitrosopyrimidines (96) undergo potassium acetate catalysed reactions with N-acylmethylpyridinium salts (97) to give the pteridine N-oxides (99) presumably via an open-chain nitrone intermediate (98). In analogous reactions (Scheme 26) amino-nitrosopyrimidines (100) condense with N-cyanobenzylpyridinium benzenesulphonates (101) in the presence of sodium cyanide, to give the pteridine N-oxides (103). These workers⁵⁰ also demonstrated that the N,N-diacetyl derivative of the triaminopyrimidine (100, $R=R^1=NH_2$) reacts in an analogous manner (Scheme 26) but the rate of cyclisation to the pteridine N-oxides (103) is much faster. This rate enhancement is considered to be due to the enhanced reactivity of the nitroso function, with acylation decreasing interactions between amino and nitroso groups.

Synthetic routes to fervenulin 4-N-oxides (106) and toxoflavin 4-N-oxides (108) have been extensively investigated by Yoneda and his co-workers because of the potential biological activity of these molecules. The 4-N-oxides (106) and (108) cannot be obtained by direct peracid oxidation (Scheme 27) of the parent bases, fervenulin (104) and toxoflavin (107), under these conditions the observed product for fervenulin (104a) is the 1-N-oxide (105a).^{51,52} Yoneda et al. initially showed⁵² (Scheme 28) that the hydrazones (109) react with aqueous sodium nitrite, in the presence of two equivalents of diethyl azodicarboxylate, to give toxoflavin 4-N-oxides (108) in low yield.



Scheme 30



(i) HCO_2H , heat.

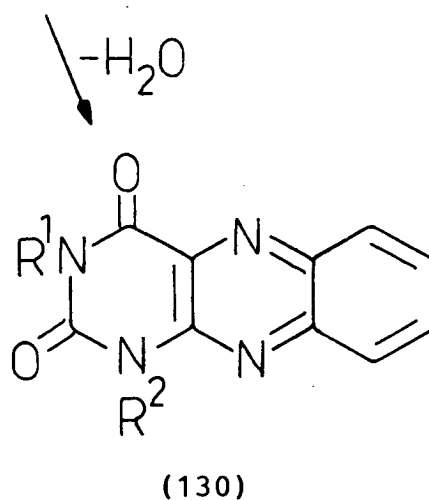
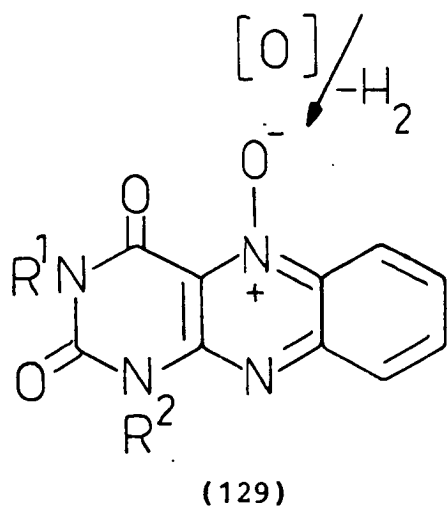
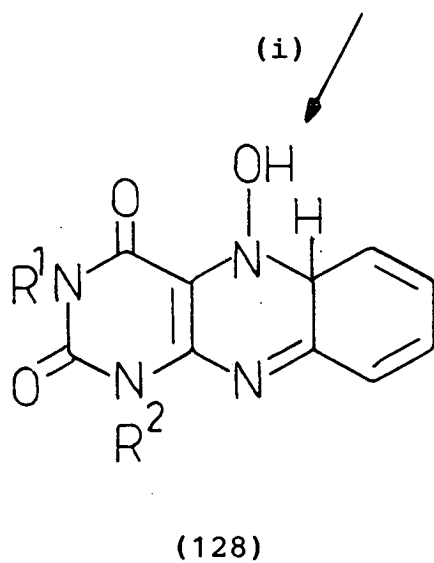
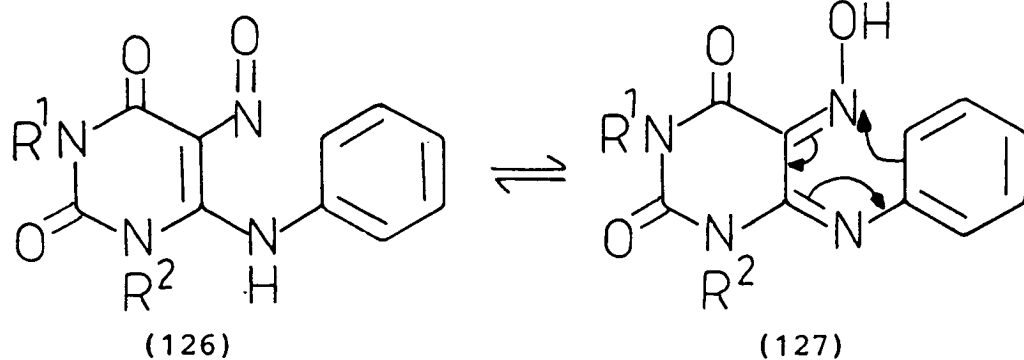
(R=H, Me, Et)

(ii) RCH(OEt)_3 , heat.

Scheme 31

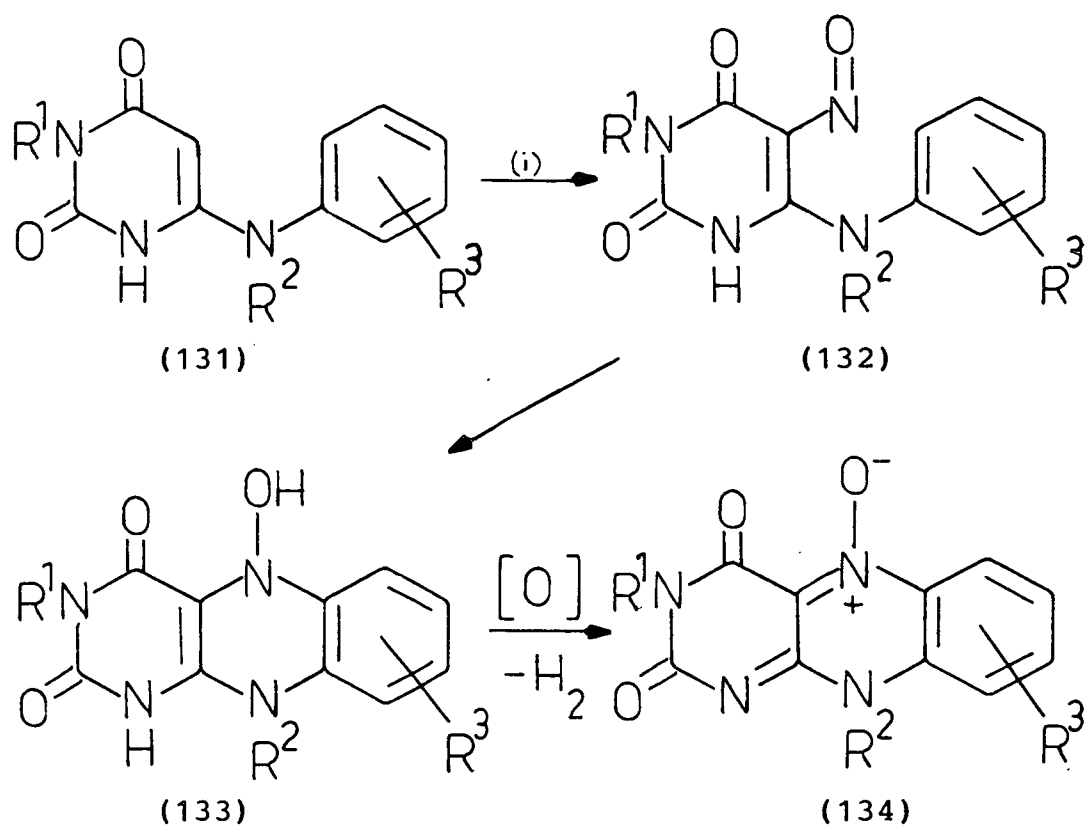
It is postulated⁵² that these reactions occur via intermediate N-hydroxy derivatives (110) which are dehydrogenated in situ to the N-oxides (108) by diethyl azodicarboxylate. It was also shown⁵² (Scheme 29) that fervenulin 4-N-oxides (106) can be prepared from suitably substituted pyrimidinedione hydrazones (111) by the same reaction and it was later shown (Schemes 28 and 29) that diethyl azodicarboxylate could be replaced in such cyclisations by diethyl azodiformate. A number of fervenulin and toxoflavin 4-N-oxides (106) and (108) were prepared using this alternative method.

Fervenulin 4-N-oxide (106a) has also been synthesised (Scheme 30) by the reaction of 1,3-dimethyl-6-hydrazino-5-nitrosouracil (113) with the Vilsmeier reagent (115).⁵¹ The mechanism (Scheme 30) proposed⁵¹ for this transformation involves reaction of the nitrosopyrimidine (113) in the oxime tautomeric form (114) with the Vilsmeier reagent (115) to give the adduct (116) and further, the protonated nitrone (117), cyclisation of which yields fervenulin 4-N-oxide (106a). An alternative mechanism (Scheme 30) for this one step synthesis of fervenulin 4-N-oxide (106a) has been suggested by Senga et al.⁵⁴ whereby reaction of the nitroso-uracil (113) with the Vilsmeier reagent (115) gives the hydrazone intermediate (121), cyclisation of which yields the N-oxide (106a) directly. It was also shown⁵⁴ that the nitroso-uracil (113) reacted with a dimethylformamide-dimethylsulphate complex, related to the Vilsmeier reagent (115), in an analogous manner to afford fervenulin 4-N-oxide (106a) in a slightly lower yield. Senga et al.⁵⁴ demonstrated (Scheme 31) another route to fervenulin 4-N-oxide (106a) by reaction of the nitroso-uracil (113) with formic acid under



	<u>R¹</u>	<u>R²</u>
a;	Me	Me
b;	H	Me
c;	Me	H

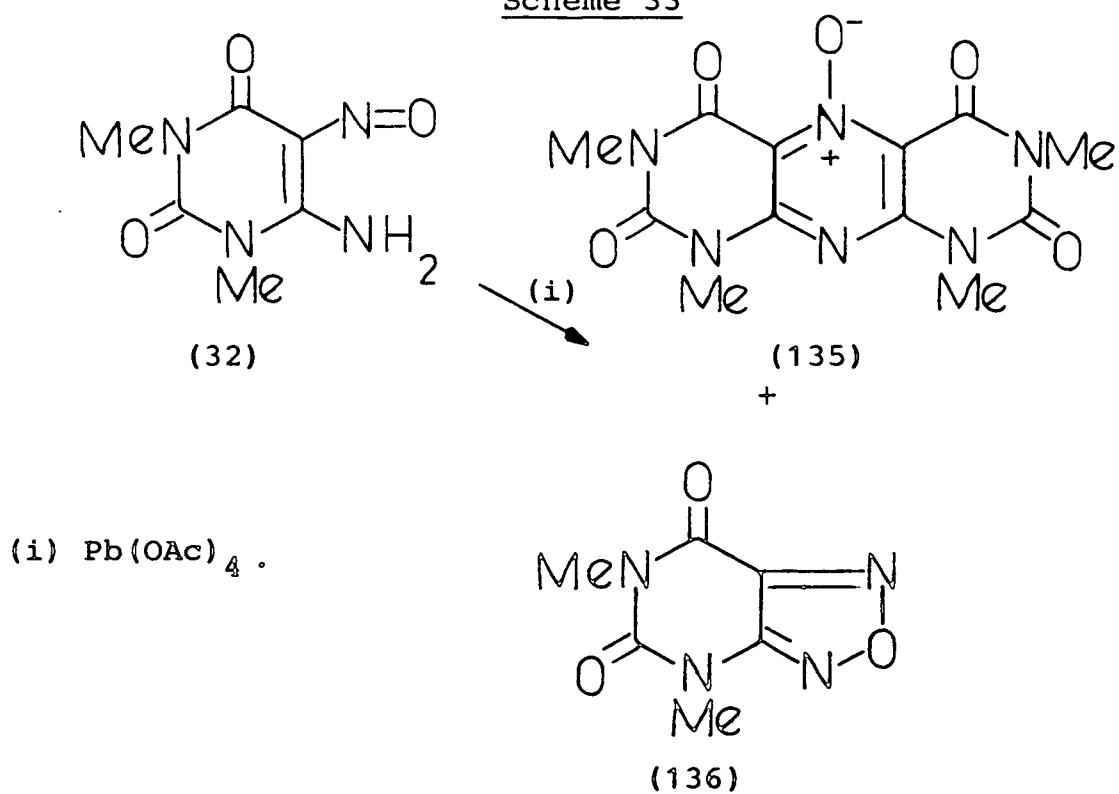
(i) isoamylnitrite, HCl, H₂O.



(i) NaNO_2 , AcOH .

	$\underline{R^1}$	$\underline{R^2}$	$\underline{R^3}$
a;	H	Me	H
b;	H	D-Ribityl	7,8-Me ₂

Scheme 33



Scheme 34

reflux. This cyclisation presumably involves the dehydrative cyclisation of a formylhydrazino intermediate (122), which is formed by the reaction of the nitroso-uracil (113) in its oxime tautomeric form (114) with formic acid. A more general synthetic route to fervenulin 4-N-oxides (106) described (Scheme 31) by these workers⁵⁴ involves the nitroso-uracil (113) reacting with triethyl orthoesters to give the N-oxides (106) possibly by way of α -ethoxyalkylidenehydrazino intermediates (124). It was also demonstrated⁵⁴ that reduction of the fervenulin 4-N-oxides (106) with sodium hydrosulphite gives the parent fervenulin derivatives.

Goldner, Dietz and Carstens⁵⁵ have reported the synthesis (Scheme 32) of benz-fused pteridine N-oxides, namely alloxazine 5-N-oxides (129) and the parent alloxazines (130), in 50-60% yield by simultaneous cyclodehydration-oxidation of 6-anilino-5-nitrosouracil derivatives (126) using isoamyl nitrite in the presence of hydrochloric acid. These authors⁵⁵ propose a mechanism for these reactions involving cyclisation of the anilino-nitrosopyrimidines (126) in the oxime tautomeric forms (127), to give cyclic hydroxylamine intermediates (128), which can either undergo oxidation to give the alloxazine 5-N-oxides (129) or dehydrate to give the parent alloxazines (130).

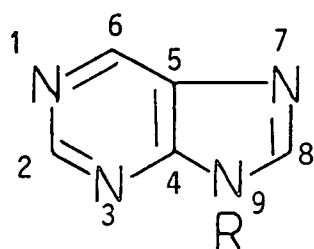
Yoneda and his co-workers⁴⁶ reported a synthesis (Scheme 33) of isoalloxazines, including riboflavin; involving reduction of the corresponding 5-N-oxides (134) which were prepared by nitrosative cyclisation of N-alkylanilinouracils (131). Thus, (Scheme 33) nitrosation of these compounds with excess sodium nitrite in glacial acetic acid affords the isoalloxazine 5-N-oxides (134) in good yields, presumably via the formation and

cyclisation of the corresponding nitroso intermediates (132). These are presumed to cyclise to the hydroxylamines (133), aerial oxidation of which would account for the formation of the N-oxides (134). These compounds can be reduced by sodium dithionite to give the parent flavins which can be reoxidised by meta-chloroperbenzoic acid to give the N-oxides (134). However, riboflavin cannot be so oxidised to the 5-N-oxide (134b). Therefore, the nitrosative cyclisation reported by Yoneda et al.⁴⁶ is an important method for the synthesis of riboflavin N-oxide (134b).

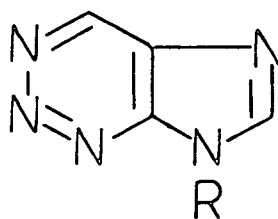
Taylor, Maki and Mckillop⁵⁶ observed (Scheme 34) the curious dimerisation of the 6-amino-5-nitrosouracil (32) in the presence of lead tetraacetate to give the pyrimido[5,4-g]-pteridinetetraone 10-N-oxide (135) together with a low yield of the expected furazano[3,4-d]pyrimidinedione (136). It was shown⁵⁶ that the pteridinetetraone 10-N-oxide (135) could be reduced to the parent pteridinetetrone using sodium dithionite.

CHAPTER TWO

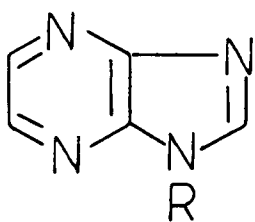
New Synthetic Approaches to N-Oxygenated Purines and Structurally Related N-Oxygenated Polyazaheterocycles Based on Nitro-group Ortho-side-chain Interaction



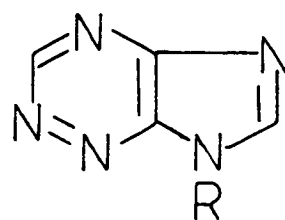
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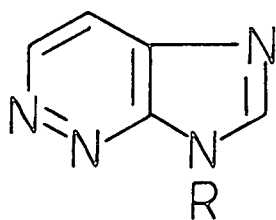
(2)



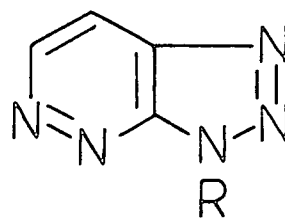
(3)



(4)

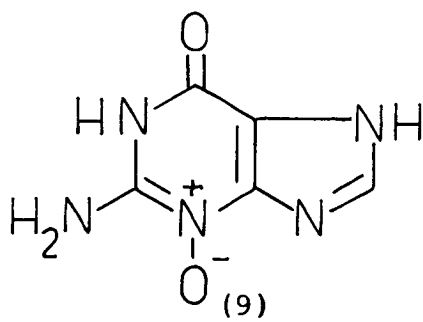
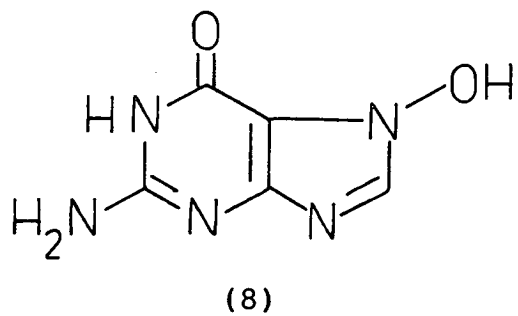
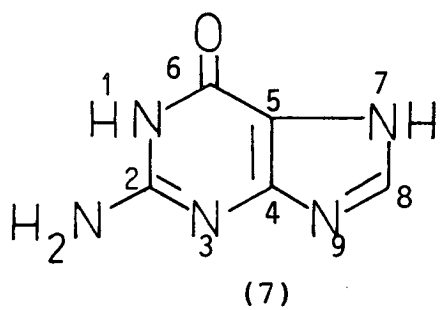


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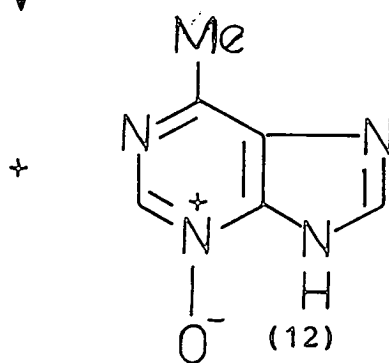
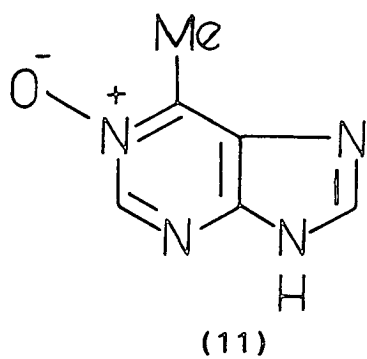
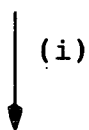
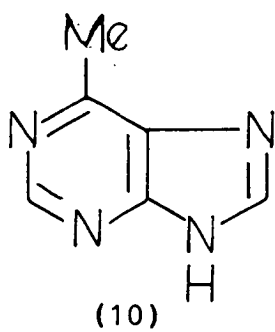


(6)

Scheme 1



Scheme 2



(i) $\underline{m}\text{-ClC}_6\text{H}_4\text{CO}_3\text{H}$.

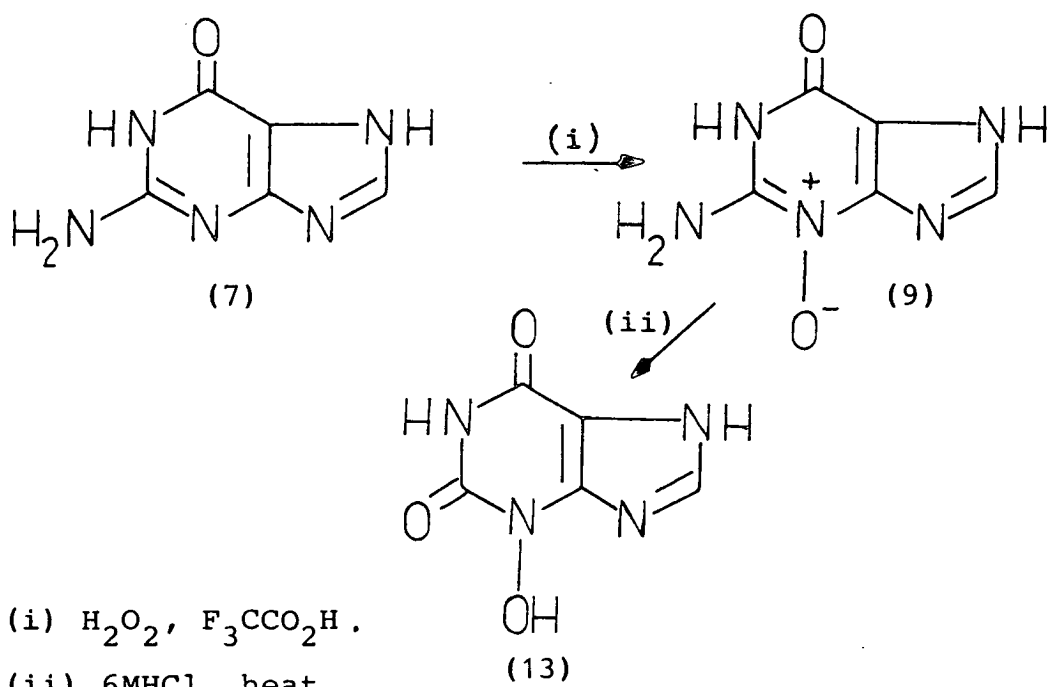
Scheme 3

New Synthetic Approaches to N-oxygenated Purines and Structurally Related N-oxygenated Polyazaheterocycles Based On Nitro-group Ortho-side-chain Interaction

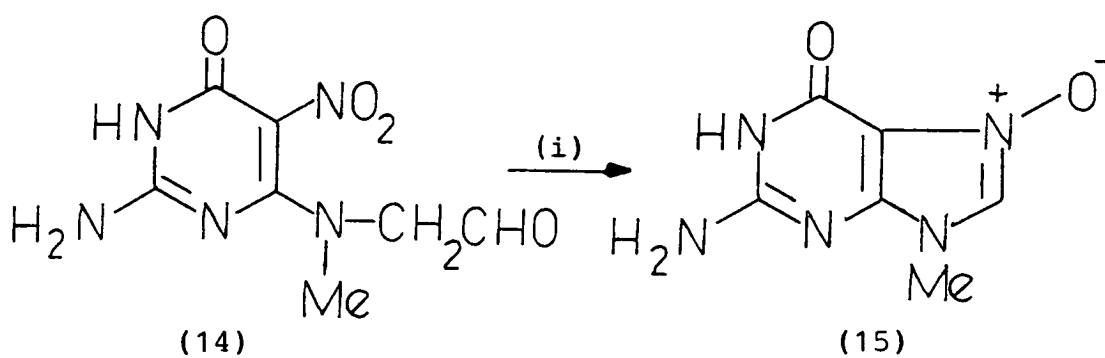
The following chapter describes investigations into new, general synthetic approaches (Scheme 1) to N-oxygenated derivatives of purines (1), imidazo[4,5-d]-1,2,3-triazines (2-aza-purines) (2) and the isosteric polyazaheterocycles, imidazo[4,5-b]pyrazines (3), imidazo[4,5-e]-1,2,4-triazines (4), imidazo[4,5-c]pyridazines (5) and 1,2,3-triazolo[4,5-c]pyridazines (6). The stimulus for these investigations was the potential biological activity of such compounds. Thus, as already discussed in the foreword, various N-oxygenated purines show pronounced oncogenic properties. For example (Scheme 2) the 7-hydroxy (8)¹² and 3-N-oxide (9)¹¹ derivatives of guanine (7) have been shown to produce tumours, in contrast to the parent system (7) which shows no such activity. Many 2-aza-purine derivatives (2) show antimetabolite action in microbiological systems⁵⁷ and 8-azaguanine has been shown to inhibit the growth of certain carcinomas and sarcomas of animals, as well as that of lymphoid leukemia in mice.

In general the N-oxides of ring systems of the types (1)-(6) are predictably much more reactive than the parent heterocycles. Purine N-oxides in particular are known²⁷ to show enhanced reactivity to nucleophilic displacement reactions at ring positions adjacent to the N-oxide substituent. This is due to the increased electrophilic character of these ring positions induced by the N-oxide group.

Although direct oxidation of ring systems of the types

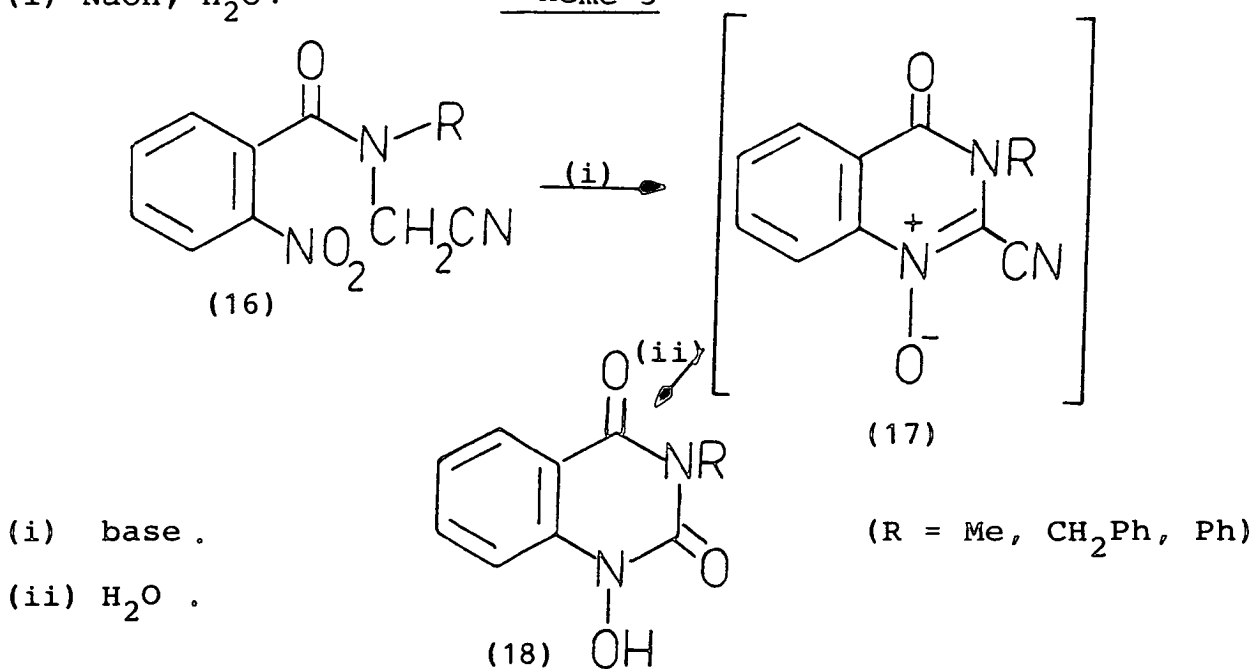


Scheme 4



(i) NaOH , H_2O .

Scheme 5



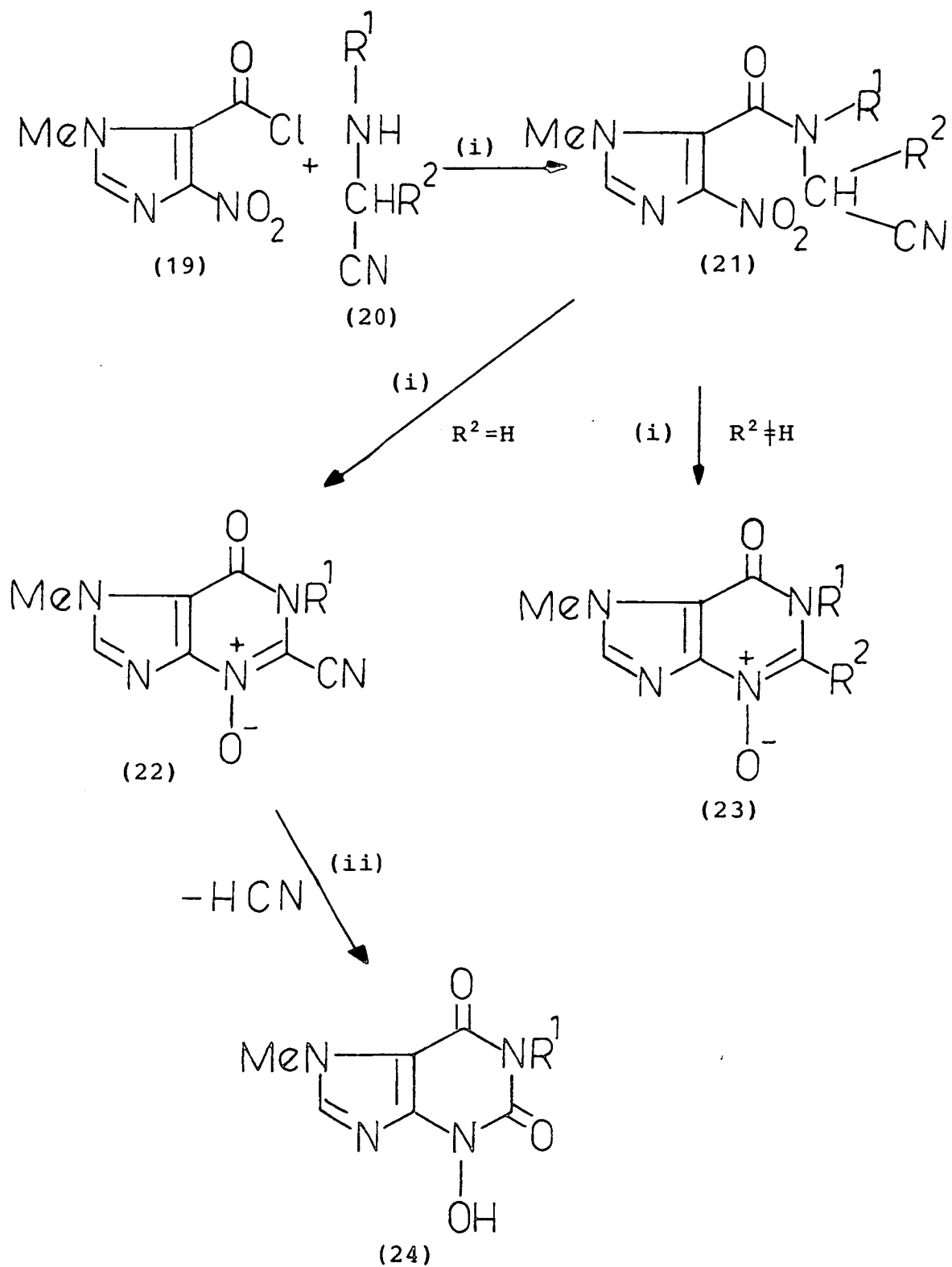
Scheme 6

(1)-(6) is of potential value²⁷ for the synthesis of certain 1-N-oxides and 3-N-oxides, its usefulness is limited by the fact that ring substituents may be hydrolysed under the acidic conditions usually employed. Also, the site of oxidation may be non specific, as in the case (Scheme 3) of 6-methylpurine (10), which affords a mixture of the 1-N-oxide (11) and the 3-N-oxide (12) on oxidation with meta-chloroperbenzoic acid. Xanthine 3-N-oxide [Scheme 4, (13)]²⁷ cannot be obtained by direct oxidation. However it may be prepared by prolonged heating of the readily obtainable guanine 3-N-oxide (9) in hydrochloric acid, further demonstrating the enhanced reactivity of N-oxygenated purines compared with the parent purines.

The synthesis of N-oxygenated purines and related heterocyclic systems by cyclisation reactions based on nitro-group ortho-side-chain interaction has been reviewed in chapter 1 and provide an attractive alternative general synthetic method to such N-oxygenated heterocycles. Perhaps the simplest example (Scheme 5)³⁰ of such a cyclisation is that of the 5-nitropyrimidin-4-ylaminoacetaldehyde (14) under alkaline conditions to give 9-methylguanine 7-N-oxide (15) in quantitative yield.

(i) Investigations of New Synthetic Approaches to N-Oxygenated Purines

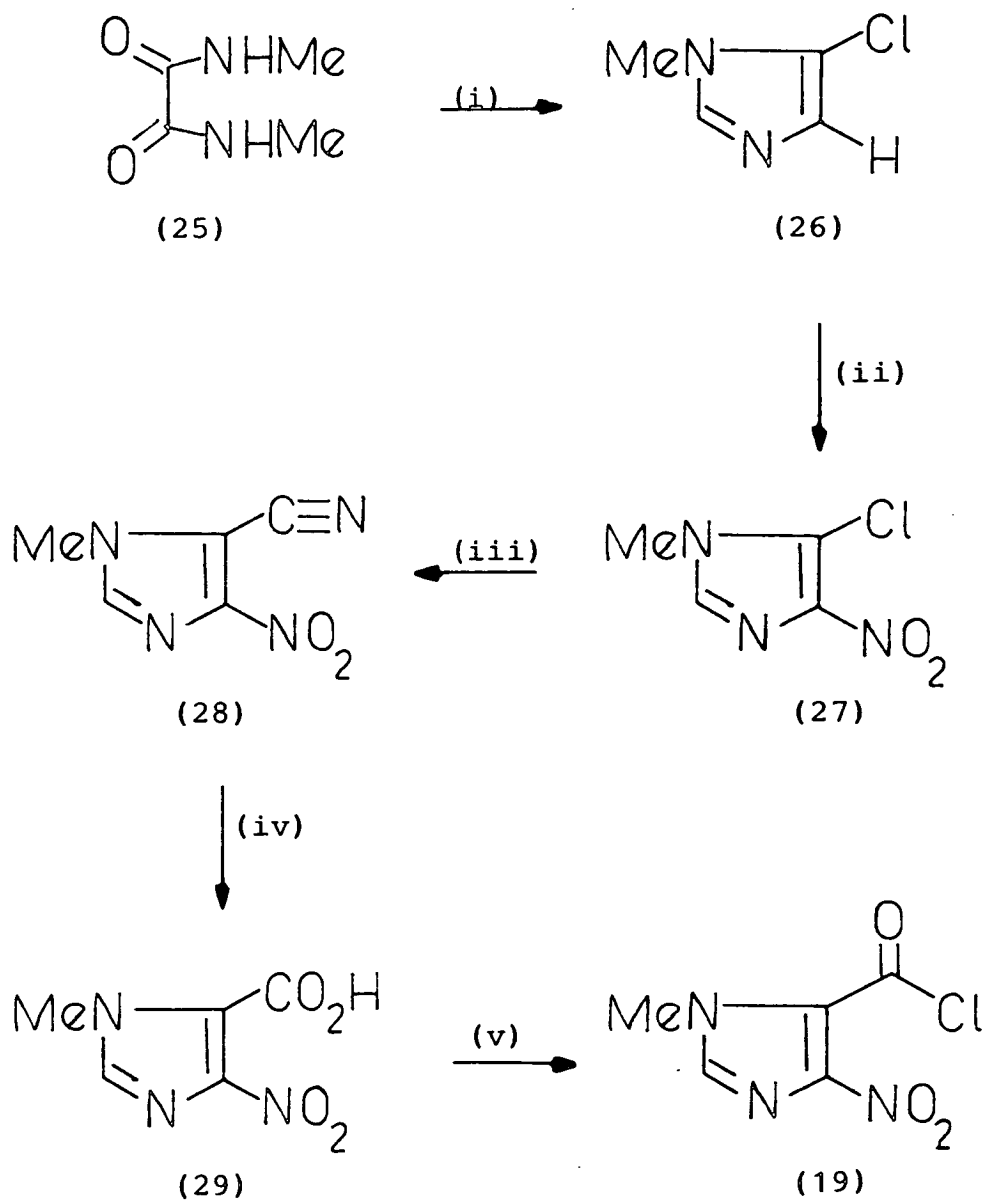
High yields (Scheme 6) of 1-hydroxyquinazoline-2,4-diones (18) are obtained⁴³ by heating N-substituted ortho-nitro-benzoylaminoacetonitriles (16) under reflux with ethanolic sodium ethoxide. The 2-cyanoquinazoline N-oxides (17) have



(i) base.

(ii) H_2O .

Scheme 7



(i) PCl_5 .

(ii) HNO_3 , H_2SO_4 .

(iii) KCN .

(iv) NaNO_2 , H_2SO_4 .

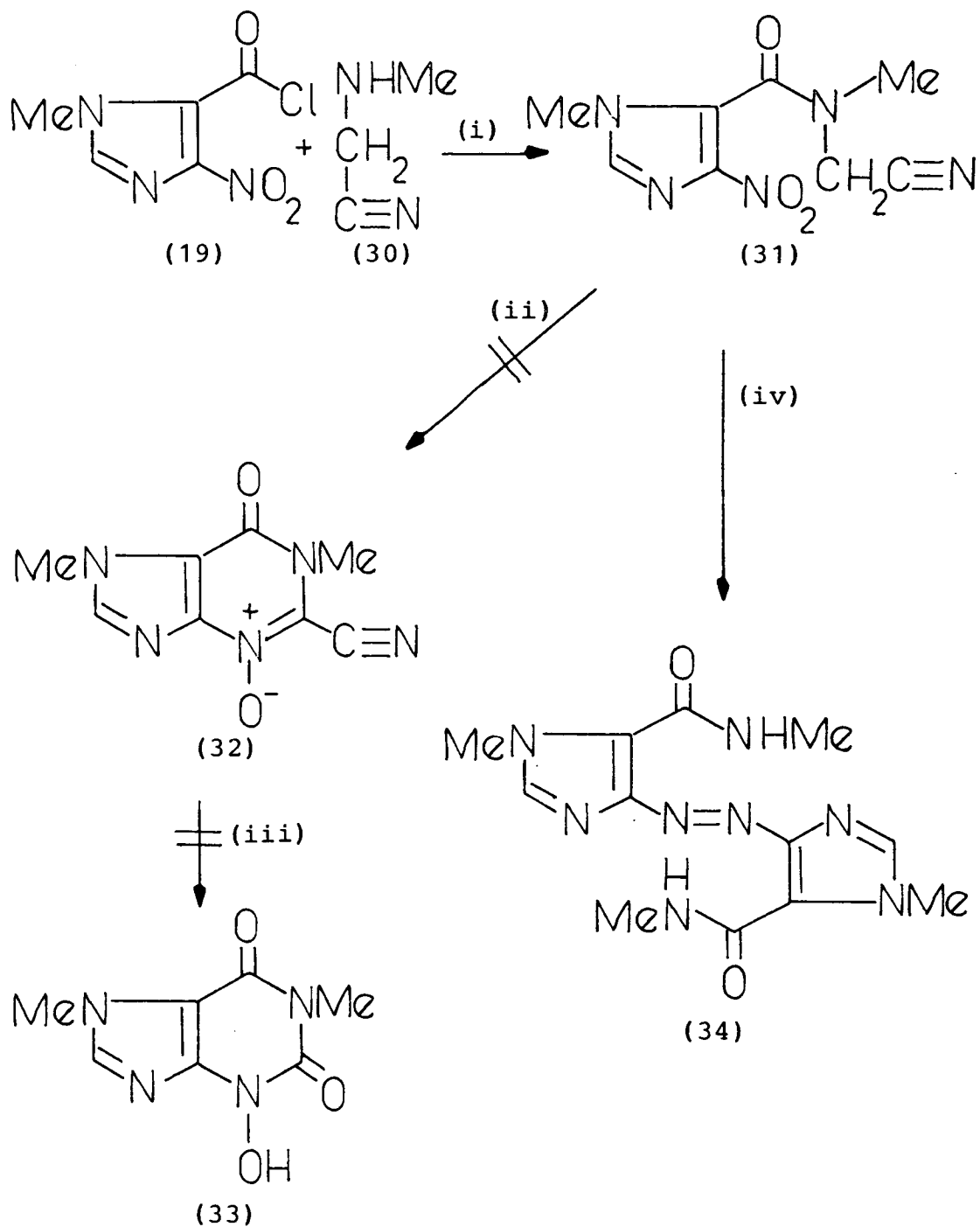
(v) SOCl_2 , reflux.

Scheme 8

been postulated as probable intermediates in these novel intramolecular aldol-type cyclisations, in which the nitro-group functions as the electrophilic centre²⁹ in the cyclisation process.

Such base-catalysed heterocyclisations could provide a very useful general synthetic route (Scheme 7) to otherwise inaccessible N-oxygenated purine derivatives (22) and (23). Thus the reaction of N-substituted aminoacetonitriles (20) with the readily available⁵⁸ 1-N-methyl-4-nitroimidazole-5-carbonyl chloride (19) should afford the N-substituted imidazole-carboxamides (21). By analogy with the N-cyanomethyl-2-nitrobenzamides (16) these imidazole-carboxamides (21) are potentially capable of undergoing base-catalysed cyclisation to the desired N-oxygenated purines (22) and (23), and in the case of the former by further transformation in the basic medium into the novel purine cyclic hydroxamic acids (24).

The key starting material for this new synthetic approach to N-oxygenated purines was 1-N-methyl-4-nitroimidazole-5-carbonyl chloride (19),⁵⁸ which was synthesised as outlined in Scheme 8. The preparation of the acid chloride (19) starts from N,N-dimethyloxamide (25) which is cyclised^{59,60} to 5-chloro-1-N-methyylimidazole (26) in moderate yield by treatment with phosphorus pentachloride. The mechanism of this novel imidazole synthesis, which was first reported by Wallach^{59,60} in 1877 is unknown. The 5-chloro-1-N-methyylimidazole (26) so obtained was readily nitrated⁶¹ to give 5-chloro-1-N-methyl-4-nitroimidazole (27). Nucleophilic displacement of the activated chlorine substituent in the chloro-nitro-imidazole (27) with cyanide afforded 5-cyano-1-N-methyl-4-nitroimidazole (28).⁶¹



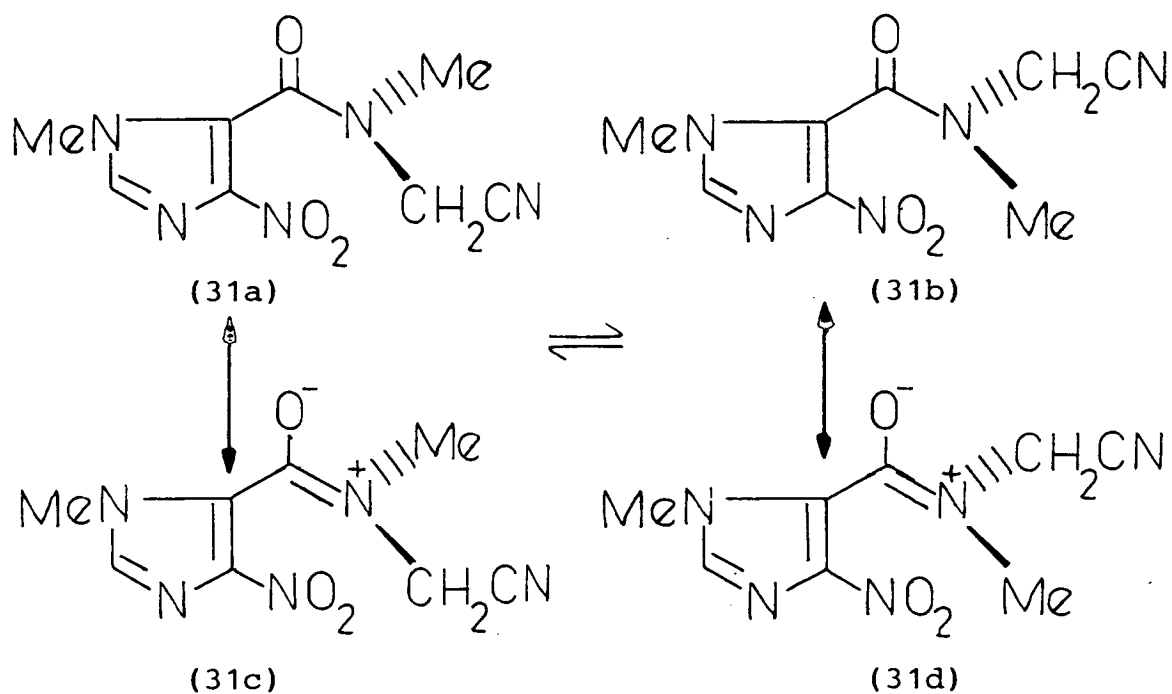
(i) AcOH, NaOAc.

(ii) base.

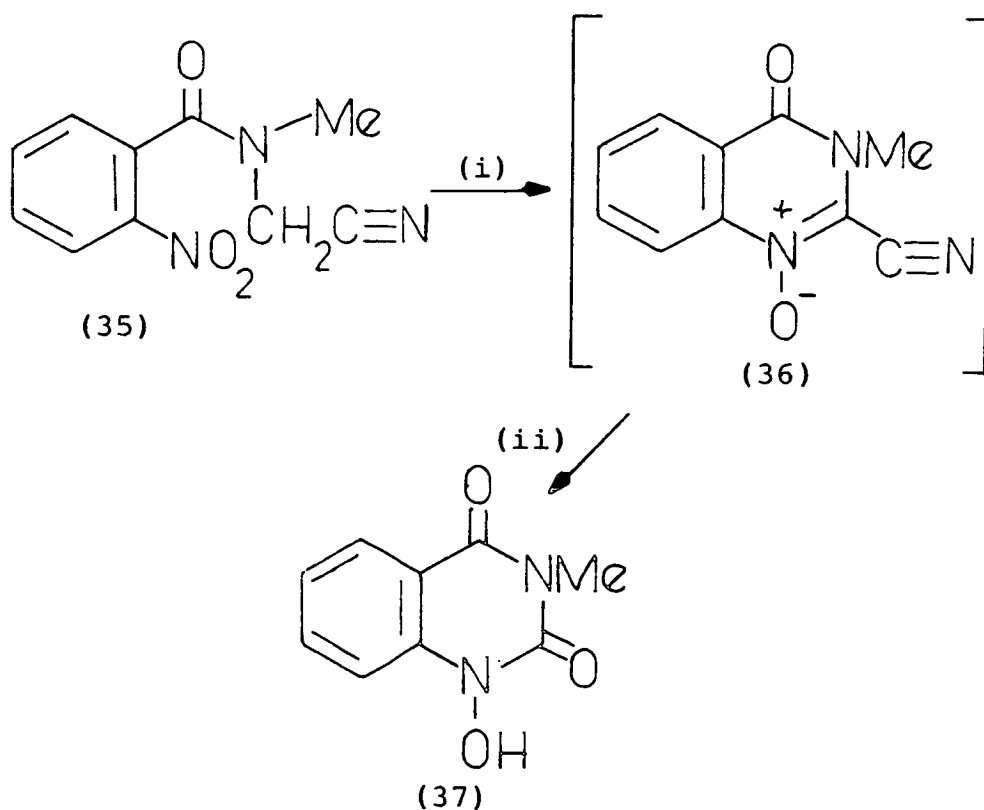
(iii) H₂O.

(iv) NaOEt, heat.

Scheme 9



Scheme 10



(i) NaOEt, heat.

(ii) H₂O.

Scheme 11

The latter was smoothly hydrolysed⁵⁸ to the required 1-N-methyl-4-nitroimidazole-5-carboxylic acid (29) which reacted readily with thionyl chloride⁵⁸ to give the acid chloride (19) in high yield. The acid chloride (19) is very unstable and must be used immediately after its preparation.

The reaction (Scheme 9) of the nitro-imidazole-carbonyl chloride (19) with methylaminoacetonitrile hydrochloride (30) in glacial acetic acid in the presence of fused sodium acetate afforded a colourless crystalline solid in high yield which gave analytical and mass spectral data consistent with the expected N-cyanomethylcarboxamide structure (31). The spectroscopic properties of this product were also consistent with the proposed structure (31). Its i.r. spectrum contained an amide carbonyl band at 1660 cm^{-1} and absorptions at 1515 and 1325 cm^{-1} due to a nitro group, but lacked any absorption due to a cyano-substituent. However it is known⁶² that i.r. cyano absorption can be very weak or totally non-observed in some cyano-compounds. The ^1H n.m.r. spectrum of the compound (31) at room temperature showed signals due to the protons of three N-methyl groups and not two as expected for the proposed structure (31). However at 90° only signals due to two N-methyl groups were observed and the phenomenon at room temperature can be attributed to restricted rotation about the amide bond as illustrated in Scheme 10. Thus the three N-methyl signals observed at room temperature are due to the conformational isomers (31a) and (31b) being "locked" in their respective spacial arrangements due to restricted rotation about the amide bond as a result of resonance [(31a) \leftrightarrow (31c); (31b) \leftrightarrow (31d)]. At 90° the temperature is high enough to

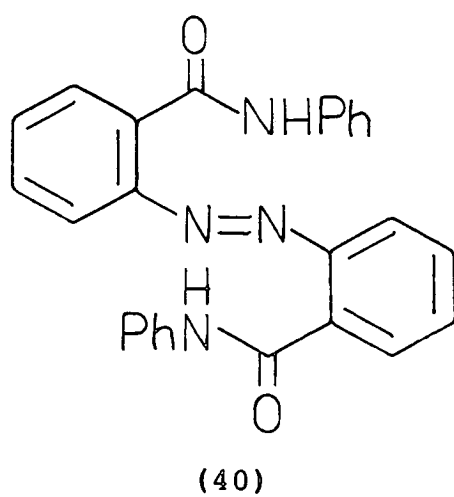
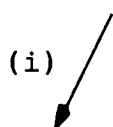
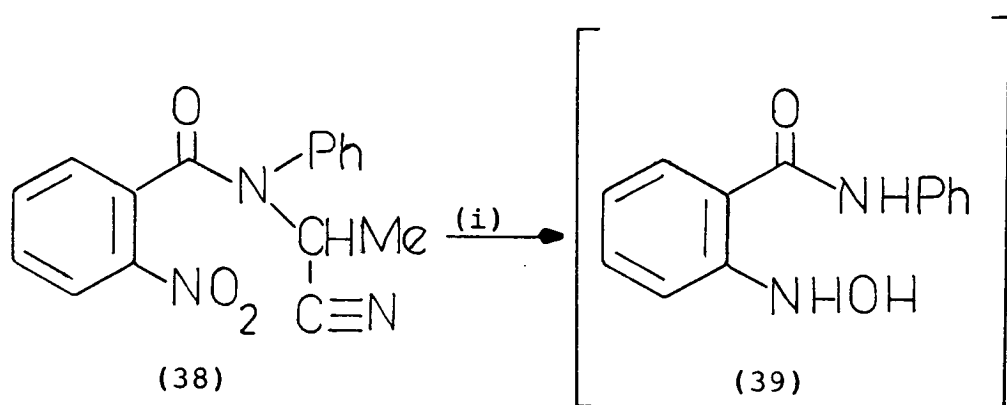
overcome the energy barrier to free rotation about the amide bond and only two N-methyl signals are observed. The ^{13}C n.m.r. spectrum of the compound was also consistent with the 1-N-methyl-4-nitroimidazole-5-(N-cyanomethyl, N-methyl) carboxamide structure (31). The off resonance ^{13}C n.m.r. spectrum showed a signal at δ_{C} 159.77 attributable to the carbonyl group and signals at δ_{C} 143.10, 138.47, 125.40, 115.76, 35.7, 35.16 and 33.202 for C-4, C-2, C-5, the nitrile, the methylene and the two N-methyl carbons respectively. The fully coupled ^{13}C n.m.r. spectrum confirmed these assignments by showing the expected multiplicity.

The expected products (Scheme 9) of the base-catalysed cyclisation of the 5-nitroimidazole-carboxamide (31) were the N-oxygenated purine derivatives (32) and/or (33). Tennant and Spence⁶³ (Scheme 11) have shown that the ortho-nitrobenzamide analogue (35) cyclises on treatment with sodium ethoxide to give the 1-hydroxyquinazoline-2,4-dione (37) in good yield. It was suggested⁶³ that this cyclisation involves the intermediate formation of the cyano N-oxide (36) which was converted into the observed hydroxamic acid product (37) in the basic medium. In the present studies it was considered that the cyclisation of the nitro-imidazole-carboxamide (31) could be controlled to afford the desired purine N-oxide (32).

Heating the 5-nitroimidazole-carboxamide (31) under reflux with sodium ethoxide in ethanol afforded a moderate yield of a yellow solid which gave analytical data consistent with the molecular formula $\text{C}_{12}\text{H}_{16}\text{N}_8\text{O}_2$. This was further substantiated by the mass spectrum which contained a parent ion at m/e 304. The i.r. spectrum of the product showed absorption at 3290

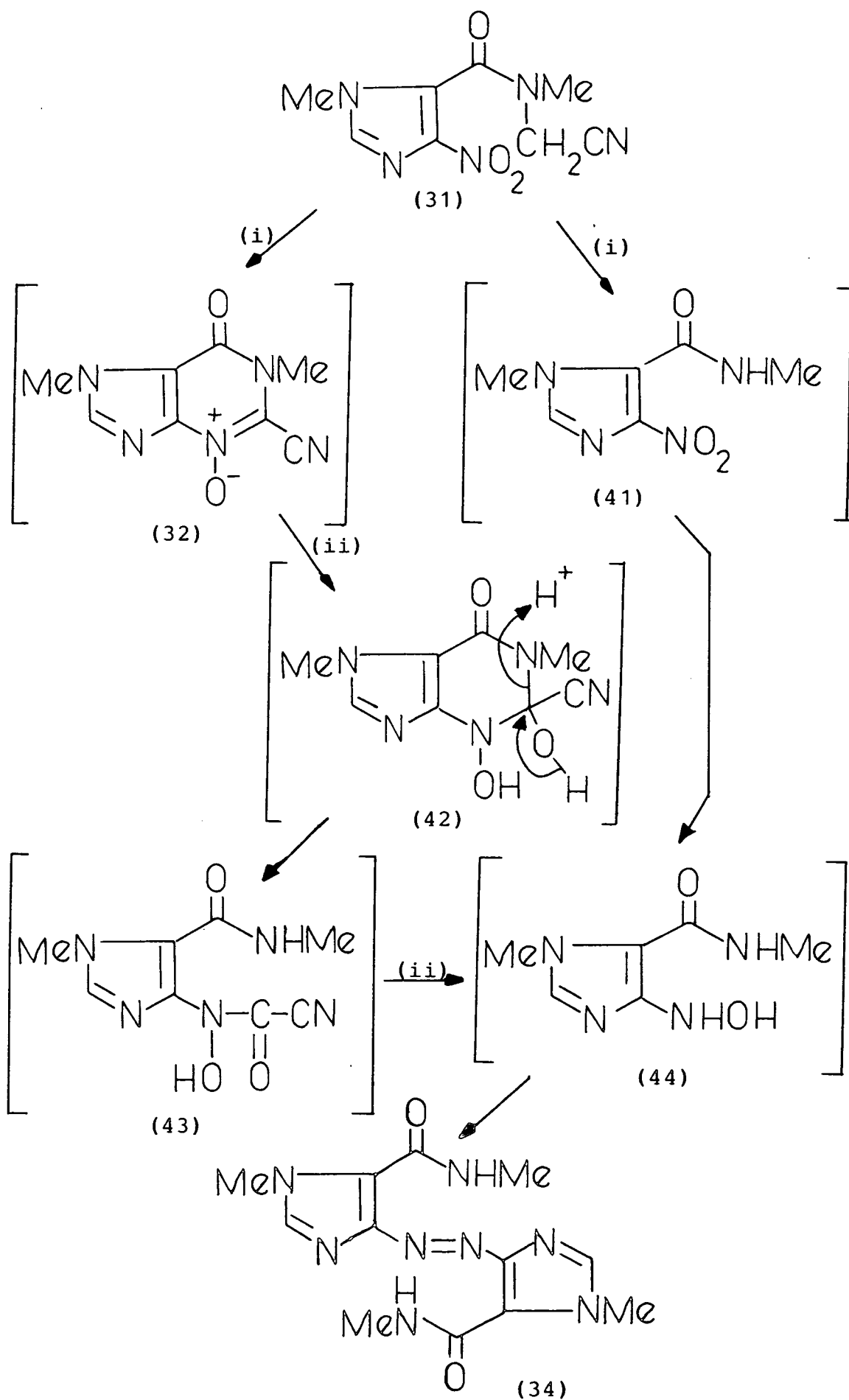
and 1660 cm^{-1} attributable to the NH and carbonyl absorption of a secondary amide substituent. The ^1H n.m.r. spectrum of the compound exhibits resonances characteristic of an imidazole ring proton and the protons of an imidazole ring N-methyl group at $\delta 8.30$ and 3.94 respectively. A triplet at $\delta 7.94$ and four discrete three-proton singlets at $\delta 3.60$, 3.50 , 3.00 and 2.91 can be assigned to the NH and methyl protons respectively of two magnetically non-equivalent NHMe groups which also experience hindered rotation about the N-C=O bond. The operation of the latter effect was readily demonstrated by measuring the ^1H n.m.r. spectrum at elevated temperature (85°), when the four discrete three proton singlets originally at $\delta 3.60$, 3.50 , 3.00 and 2.91 were observed to coalesce to two closely spaced doublets ($J=2\text{Hz}$) centred at $\delta 3.49$ and 2.94 . The simplification of the ^1H n.m.r. absorption of the NH-CH₃ substituents at 85° can be attributed to the absence of hindered rotation at elevated temperature. The ^{13}C n.m.r. ^{spectrum} of this material was unobtainable because of its poor solubility.

The analytical and spectroscopic properties of the yellow product are entirely consistent with the azo-structure [Scheme 9; (34)] which presumably adopts a preferred conformation in which the N-methyl carboxamide groups are magnetically non-equivalent. An attempt to further verify the structure (34) for the yellow product by alkaline hydrolysis to the corresponding carboxylic acid was unsuccessful. Heating the product (34) under reflux with aqueous sodium hydroxide afforded only unreacted starting-material. However the formation of the azo-product (34) from the imidazole N-cyano-methylcarboxamide (31) is analogous to the known⁶³ base-catalysed



(i) Na_2CO_3 , H_2O , EtOH, reflux, 1h.

Scheme 12



(i) NaOEt, EtOH, heat.

(ii) H₂O.

transformation (Scheme 12) of the N-cyanoalkyl-2-nitrobenzamide derivative (38), via the presumed intermediacy of the hydroxyamino-amide (39), into the azo-benzamide derivative (40).

Two mechanisms (Scheme 13) can be proposed to explain the base-catalysed formation of the azo-imidazole derivative (34) from the imidazole N-cyanomethylcarboxamide (31). One possibility is that the anticipated aldol-type cyclisation to give the purine N-oxide (32) is followed by the formation of a hydrate (42), ring-opening of which could lead to a hydroxy-amino-derivative (44) capable of self-condensation to afford the observed azo-imidazole (34). Alternatively (Scheme 13) initial hydrolysis of the amide (31) could yield the nitro-imidazole-carboxamide (41), reductive dimerisation of which in the alkaline medium would then give the azo-product (34). The latter route is tentatively supported by the fact that the amide (41), which is readily available by the reaction of the acid chloride (19) with aqueous methylamine, gave a low yield of the azo-imidazole (34) when it was heated under reflux with ethanolic sodium ethoxide.

In an attempt to isolate the purine 3-N-oxide (32) proposed as a possible intermediate in the base-catalysed formation of the azo-imidazole (34) from the nitro-imidazole-carboxamide (31), the reaction of the latter with sodium ethoxide was repeated at room temperature. However under these conditions the only materials isolated were intractable brown oils which were shown by t.l.c. to be complex mixtures, and were therefore not further investigated.

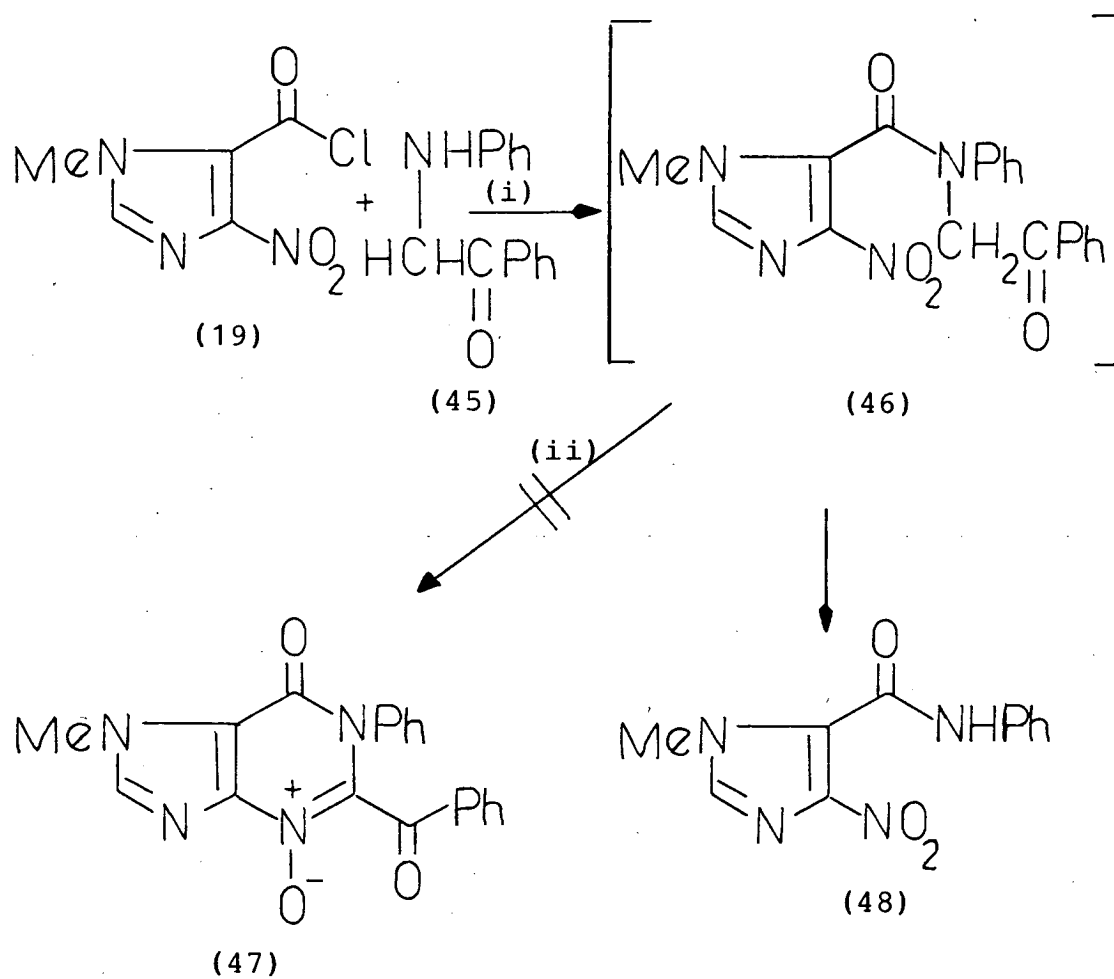
In an attempt to achieve the base-catalysed cyclisation

(Scheme 9) of the nitro-imidazole-carboxamide (31) to the N-oxygenated purine products (32) and/or (33), various other basic catalysts for the cyclisation were investigated. Thus, treatment of the nitro-imidazole-carboxamide (31) with sodium hydride gave largely intractable gums and oils together with a very low yield of a green solid product which gave analytical and mass spectral data consistent with the molecular formula $C_{11}H_{12}N_8O_2$. The i.r. spectrum of the green product, in addition to showing NH and carbonyl absorption at 3360 and 1660 cm^{-1} respectively, also exhibited a band at 2200 cm^{-1} attributable to the presence of a cyano-group. Lack of material prevented the further characterisation of this minor product. However from its analytical and spectroscopic properties it was clearly neither of the expected N-oxygenated purines (32) and (33), and because of this, and its low yield, no attempt was made to further characterise it.

Since the lack of formation of the N-oxygenated purines (32) or (33) from the nitro-imidazole-carboxamide (31) using sodium ethoxide or sodium hydride as the basic catalyst could be due to their further transformation under the strongly basic reaction conditions employed, it was next decided to investigate the more weakly basic sodium carbonate as the catalyst. In practice, heating the nitro-imidazole-carboxamide (31) with sodium carbonate in aqueous ethanol afforded a yellow product whose combustion analysis was not consistent with either of the desired N-oxygenated purine structures (32) or (33). The combustion analysis of the compound was however consistent with the molecular formula $C_{11}H_{12}N_8O_2$ which was further substantiated by the presence of a parent ion at m/e 288 in its

mass spectrum. However the compound's i.r. spectrum contained only carbonyl absorption and was not identical to that of the isomeric product obtained from the action of sodium hydride on the nitro-imidazole-carboxamide (31). The compound's ^1H n.m.r. spectrum, in addition to having a three-proton singlet at $\delta 3.94$ assignable to an imidazole N-methyl group, also contained a three-proton doublet and a one-proton triplet at $\delta 2.88$ and 7.94 attributable, respectively, to the methyl and NH protons of a methylamino substituent. Significantly however it lacked a one-proton resonance at ca. $\delta 7.9$ due to an imidazole ring proton. This indicates the absence of an intact imidazole nucleus in the unknown compound and implies that hydrolytic ring-opening of the imidazole ring in the original nitro-imidazole carboxamide (31) must have occurred on treatment with aqueous ethanolic sodium carbonate. The unknown compound was too insoluble for its ^{13}C n.m.r. spectrum to be measured thus preventing further structural information on the compound being obtained spectroscopically. Because of the limited amount of material available, and the apparent absence of an intact imidazole ring in the unknown compound no attempt was made to further characterise this material.

Having failed to achieve the base-catalysed cyclisation of the nitro-imidazole-carboxamide (31) to either of the N-oxygenated purine derivatives (32) or (33) using metallic bases as catalysts, attention was next turned to the attempted cyclisation of the nitro-imidazole derivative (31) using amine bases. However heating the nitro-imidazole-carboxamide (31) under reflux with piperidine in ethanol gave only the unreacted starting-material (31) together with an unresolvable multi-



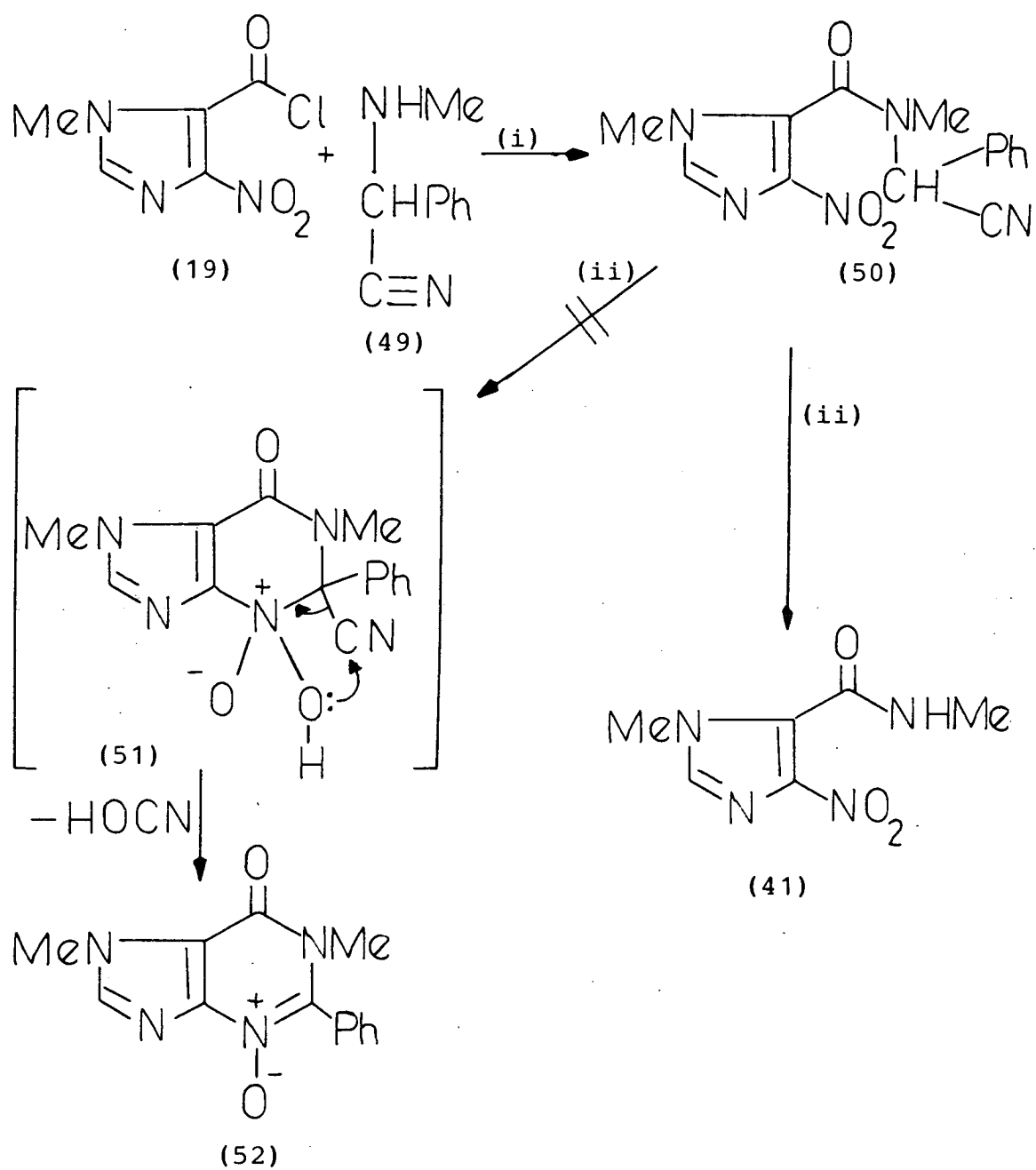
(i) NaOAc, AcOH.

(ii) base.

Scheme 14

component oil. The attempted cyclisation of the nitro-imidazole-carboxamide (31) using diazabicyclo[3,4,0]non-5-ene (DBN) as the basic catalyst was no more successful, the starting-material (31) and intractable oils being the only materials recovered after treating the amide (31) with DBN at low temperature or under reflux.

The failure of the readily available nitro-imidazole-carboxamide (31) to undergo base-catalysed cyclisation to N-oxygenated purine products using a variety of basic catalysts was disappointing and could possibly be due to complicating side reactions stemming from the tendency of the cyano-substituent to undergo nucleophilic displacement on solvolysis under the basic reaction conditions. For this reason it was decided to seek an alternative nitro-imidazole-carboxamide starting-material for N-oxygenated purine formation which might not be so prone to side-reactions under basic conditions. The nitro-imidazole-carboxamide starting-material chosen for study (Scheme 14) was the previously unknown N-phenacyl derivative (46). The benzoyl substituent in this compound should ensure the activation of the methylene substituent necessary for successful cyclisation to the N-oxygenated purine (47), while at the same time being stable to nucleophilic displacement and relatively stable to hydrolysis. It was proposed to obtain the required nitro-imidazole N-phenacylcarboxamide (46) by the condensation of the acid chloride (19) with the readily available⁶⁴ anilinoacetophenone (45). However the attempted reaction of the acid chloride (19) with the amino-ketone (45) in glacial acetic acid in the presence of sodium acetate under conditions known⁶³ to effect such amide formation gave none of the required nitro-imidazole N-phenacylcarboxamide (46). Instead the only



(i) AcOH, NaOAc.

(ii) base.

Scheme 15

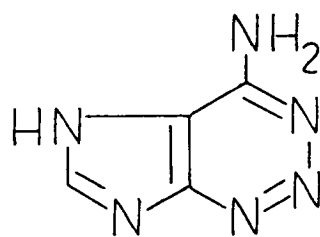
products were 1-N-methyl-4-nitroimidazole-4-N-phenylcarboxamide (48), isolated in low yield, and a red glassy solid which was shown by t.l.c. to be a complex mixture and therefore was not further investigated. The identity of the amide product (48) was established by its analytical and spectroscopic properties and its formation in the sodium acetate catalysed reaction of the acid chloride (19) with the amino-ketone (45) is presumably due to subsequent hydrolysis of the expected amide product (46). In view of the apparent facile hydrolysis of the amide (46) under the mildest possible conditions for its formation, further attempts to achieve its synthesis and of course its proposed cyclisation to the N-oxygenated purine (47) were not investigated.

Since the failure of the nitro-imidazole N-cyanomethylcarboxamide (31) to undergo base-catalysed cyclisation to N-oxygenated purines (32) or (33) can be attributed to the necessity of using relatively powerful basic catalysts because of the relatively weakly acidic nature of the methylene group in (31), it was of interest to study a nitro-imidazole-carboxamide derivative having a more acidic N-substituent. Such a carboxamide derivative might cyclise using less powerful basic catalysts. The compound chosen for study in this respect (Scheme 15) was the nitro-imidazole N-(α -phenyl) cyanomethylcarboxamide (50), which could be expected to undergo base-catalysed cyclisation with loss of the cyano-substituent⁶⁵ to afford a purine N-oxide [Scheme 15; (50) \rightarrow (51) \rightarrow (52)]. The nitro-imidazole N-(α -phenyl) cyanomethylcarboxamide (50) was readily prepared in high yield by the reaction of the nitro-imidazole-carbonyl chloride (19) with α -N-methylaminophenylacetonitrile (49) in glacial acetic acid in the presence of sodium acetate.

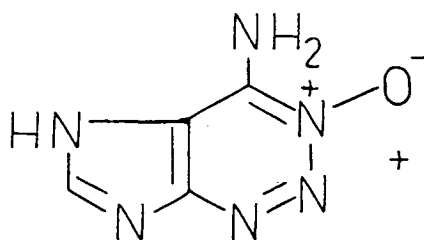
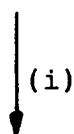
The analytical and spectroscopic properties of the imidazole derivative (50) were fully in accord with the assigned structure. Its i.r. spectrum showed an amide carbonyl band at 1665 cm^{-1} and absorption at 1525 and 1345 cm^{-1} due to a nitro-group. As in the case of the nitro-imidazole N-cyanomethylcarboxamide (31), it lacked i.r. cyano absorption. Signals at $\delta 8.0$ and 7.18 in the ^1H n.m.r. spectrum of the imidazole derivative (50) can be assigned to the imidazole ring CH and side-chain CH protons respectively.

Attempts to carry out a base-catalysed cyclisation of the nitro-imidazole-carboxamide (50) to the N-oxygenated purine derivative (52) under a variety of conditions were unsuccessful. Heating the nitro-imidazole-carboxamide (50) under reflux with aqueous ethanolic sodium carbonate afforded in addition to a small amount of unreacted starting-material (50), good yields of the hydrolysis products, 1-N-methyl-4-nitroimidazole-5-N-methylcarboxamide (41) and benzoic acid. The former product was identified by comparison with an authentic sample (see above). The hydrolytic breakdown of the nitro-imidazole N-(α -phenyl)cyanomethylcarboxamide (50) with aqueous ethanolic sodium carbonate suggested that even these relatively mild cyclisation conditions were too severe. However even heating the nitro-imidazole-carboxamide (50) with the weaker base, sodium acetate, in aqueous ethanol again afforded the hydrolysis products 1-N-methyl-4-nitroimidazole-4-N-methylcarboxamide (41) and benzoic acid, together with an intractable gum.

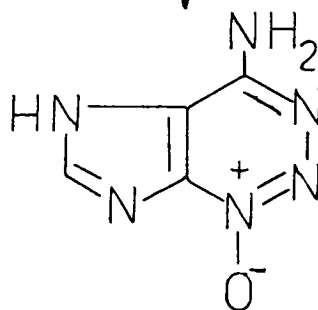
Having failed to achieve the cyclisation of the nitro-imidazole-carboxamide derivative (50) to the N-oxygenated purine (52) using both aqueous ethanolic sodium carbonate and aqueous ethanolic sodium acetate under reflux, attention was



(53)

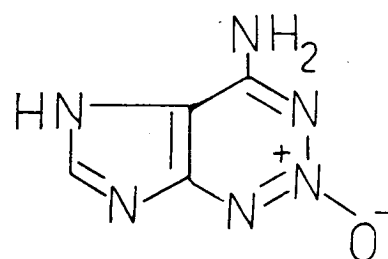


(54)



(55)

or



(56)

(i) H_2O_2 , AcOH .

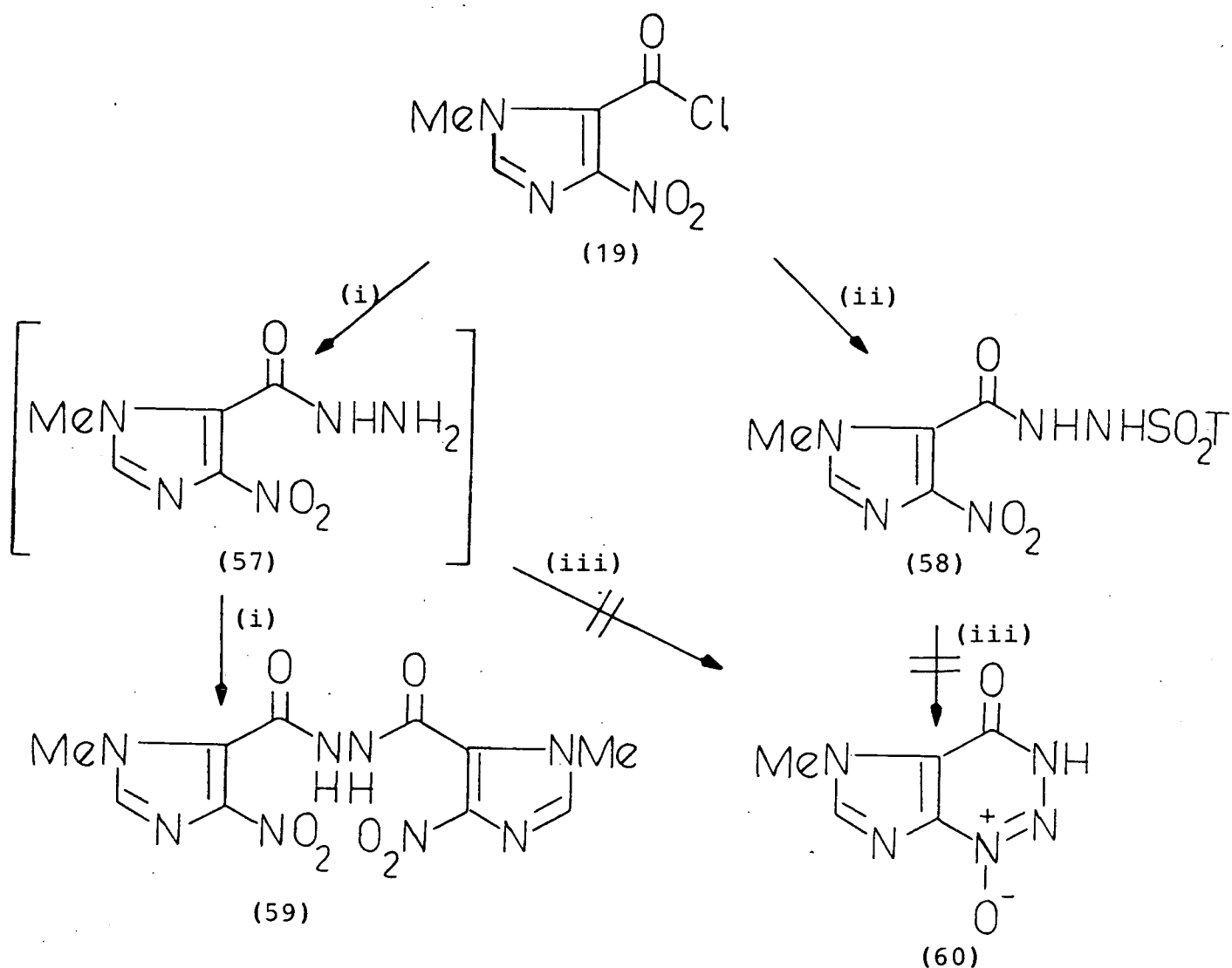
Scheme 16

next turned to the use of an amine as the cyclisation catalyst. The strongly basic but poorly nucleophilic base DBN was chosen, but treatment of the amide (50) with this reagent in dimethylformamide at ice-bath temperature afforded only the hydrolysis product 1-N-methyl-4-nitroimidazole-5-N-methylcarboxamide (41) together with dark gums, and none of the hoped for N-oxygenated purine (52).

The results obtained from the attempted base-catalysed cyclisation of the nitro-imidazole-carboxamides [Scheme 9; (31)] and [Scheme 15; (50)] indicate the inherent susceptibility of the N-C bond in the amide side-chain of such compounds to hydrolytic scission, which prevents their successful cyclisation to the desired N-oxygenated purines [Scheme 9; (32)] and [Scheme 15; (52)].

(ii) Investigations of New Synthetic Approaches to N-Oxygenated Imidazo[4,5-d]-1,2,3-triazines (2-Azapurines)

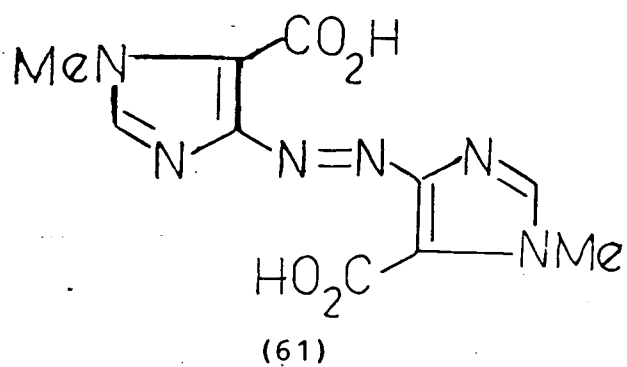
Many imidazo[4,5-d]-1,2,3-triazines (2-azapurines)⁵⁷ show antimetabolite action in microbiological systems and their synthesis from imidazole precursors has been extensively studied,⁶⁶ the first example being reported as early as 1951. Thus, Woolley and Shaw⁶⁷ described the synthesis (Scheme 16) of 2-aza-adenine (53) and the peracid oxidation of this compound which afforded a 3:1 mixture of two mono-N-oxides. The major product was shown to be the 3-N-oxide (54), but the position of the N-oxide group could not be established with certainty in the minor product which was formulated either as the 1-N-oxide (55) or the 2-N-oxide (56). Because of the structural



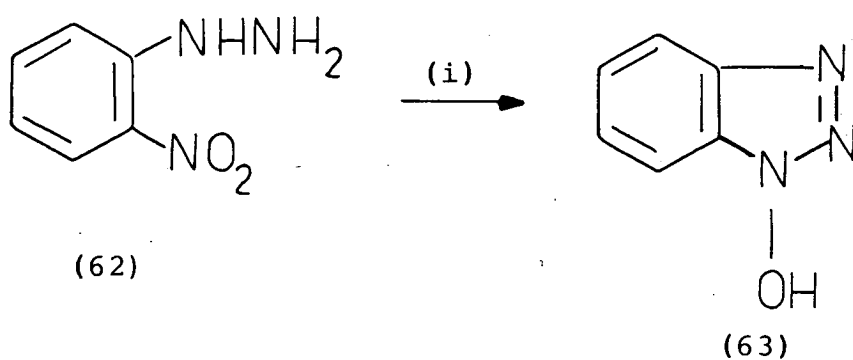
(i) NH_2NH_2 .

(ii) $\text{TSO}_2\text{NHNH}_2$, NaOAc, AcOH.

(iii) base.



Scheme 17



(i) NaOH , H_2O , heat.

Scheme 18

ambiguity of the N-oxide products, peracid oxidation of imidazo[4,5-d]-1,2,3-triazines is not a viable method for the synthesis of N-oxygenated 2-azapurines. These compounds are of interest as a result of their potential biological activity. Thus, it was of interest to investigate (Scheme 17) the previously unreported, but potentially viable, base-catalysed cyclisation of ortho-nitro-imidazoloylhydrazines [e.g. (57)] as an unambiguous method for the synthesis of N-oxygenated 2-azapurines [e.g. (60)]. This type of cyclisation would be analogous to the well known²⁹ transformation (Scheme 18) of 2-nitrophenylhydrazine (62) in warm aqueous alkali into 1-hydroxybenzo-1,2,3-triazole (63).

The key starting-material for the proposed synthetic approach (Scheme 17) to 2-azapurine 1-N-oxides [i.e. (57)] was the nitro-imidazole-carbonyl chloride (19), the synthesis of which has already been described. The reaction (Scheme 17) of this acid chloride with hydrazine monohydrate in dry dioxane under reflux did not however afford the desired imidazoloylhydrazine (57). Instead this reaction afforded a moderate yield of a yellow product which gave accurate mass data consistent with the molecular formula $C_{10}H_{10}N_8O_6$. The i.r. spectrum of this product showed amide NH and carbonyl absorption at 3140 and 1650 cm^{-1} and its 1H n.m.r. spectrum indicated the presence of the 1-N-methylimidazole nucleus with one-proton and three-proton resonances at δ 7.96 and 3.78, characteristic of the imidazole ring and NCH_3 protons respectively. These properties are consistent with the diacylhydrazine structure (59) whose formation can be ascribed to further reaction of the initially formed monohydrazide (57) with a further

molecule of the acid chloride (19). The formation of the diacylhydrazine (59) instead of the required monohydrazide (57) precluded the proposed investigation of the base-catalysed cyclisation of the latter to the 2-azapurine N-oxide (60).

Because of the complicating formation of the diacylhydrazine (59) in the reaction of the acid chloride (19) with hydrazine it was decided to investigate the alternative reaction of the acid chloride (19) with toluene-*p*-sulphonylhydrazine (tosylhydrazine) in the expectation of obtaining the tosyl derivative (58) of the elusive monohydrazide (57). The tosylhydrazide (58) has the advantage of being stable to further reaction with the acid chloride (19) under the conditions of its formation. Moreover the enhanced acidity of the tosylamino moiety in the ortho-side chain of the hydrazide (58) should facilitate its base-catalysed cyclisation, with concomitant hydrolytic loss of the tosyl substituent, to give the azapurine N-oxide (60). In practice (Scheme 17), the acid chloride (19) reacted readily with toluene-*p*-sulphonylhydrazine (tosylhydrazine) in glacial acetic acid in the presence of sodium acetate to give a colourless product whose analytical and mass spectral properties are consistent with the expected tosylhydrazide structure (58). This was also supported by the product's i.r. spectrum which showed hydrazine NH and carbonyl absorption at 3200 and 1710 cm^{-1} as well as nitro-absorption at 1510 and 1340 cm^{-1} . The ^1H n.m.r. spectrum of the tosylhydrazide (58) was also in accord with its assigned structure and in particular showed a one proton resonance at $\delta 7.86$ due to the imidazole C-2 ring proton and two three proton

singlets at δ 3.49 and 2.38 due to the imidazole N-methyl and p-tosyl C-methyl substituents respectively.

Surprisingly, despite the presence of the acidic tosylamino side-chain the tosylhydrazide (58) was exceptionally stable to attempts to effect its base-catalysed cyclisation. Thus, the reaction of the tosylhydrazide (58) under reflux in ethanol with piperidine afforded a quantitative yield of a crystalline solid whose properties are consistent with it being a simple piperidine salt of the acidic tosylhydrazide (58). In accord with this formulation, treatment of the salt with dilute hydrochloric acid effected its reconversion into the unchanged tosylhydrazide (58).

On the assumption that piperidine was an insufficiently strong base for effecting the base-catalysed cyclisation of the tosylhydrazide (58), the cyclisation of the latter using ethanolic sodium ethoxide was next attempted. However, heating the tosylhydrazide (58) under reflux with ethanolic sodium ethoxide gave only a high recovery of unreacted starting-material showing that the tosylhydrazide (58) is exceptionally stable under strongly basic conditions. This stability of the tosylhydrazide (58) under basic conditions is further demonstrated by the fact that it is recovered quantitatively when its sodium salt is subjected to prolonged heating in diethyleneglycol-dimethylether (diglyme).

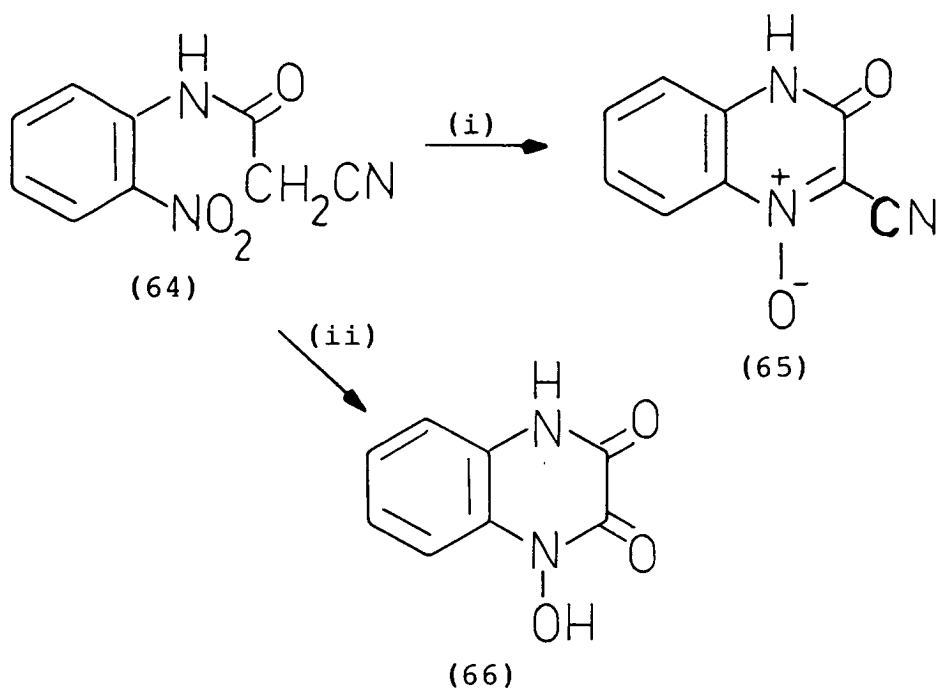
In a further attempt to effect the base-catalysed cyclisation of the tosylhydrazide (58) it was heated under reflux with 20% w/v aqueous potassium hydroxide in ethanol. This reaction afforded, together with unreacted starting-material (58) a low yield of a product whose mass spectrum showed a

parent ion at m/e 278, allowing its tentative formulation as the azo-imidazole-dicarboxylic acid (61). Lack of material prevented the further characterisation of the compound by combustion analysis and ^1H n.m.r. spectroscopy. Prolonged heating of the imidazole-tosylhydrazide (58) under reflux with aqueous potassium hydroxide also only afforded unreacted starting-material (58) together with a glassy solid and an oil whose t.l.c. showed them to be unresolvable multicomponent mixtures which were not further investigated.

The failure of the nitro-imidazole-tosylhydrazide (58) to undergo base-catalysed cyclisation to an N-oxygenated 2-azapurine (60) is surprising in view of the greater acidity of the ortho side-chain in the tosylhydrazide (58) when compared with that in 2-nitrophenylhydrazine (62) which, as already discussed, readily undergoes base-catalysed cyclisation to the 1-hydroxybenzo-1,2,3-triazole (63). The reason for the reluctance of the nitro-imidazole-tosylhydrazide (58) to undergo base-catalysed cyclisation is unclear, but may be due to the stability of the tosylamino moiety to hydrolysis, thus prohibiting the formation of a stable cyclic product and hence promoting reversal of the ring-forming step and the isolation of the unchanged starting-material (58).

(iii) Investigations of New Synthetic Approaches to N-Oxygenated Imidazo[4,5-b]pyrazines and Imidazo[4,5-e]-1,2,4-triazines

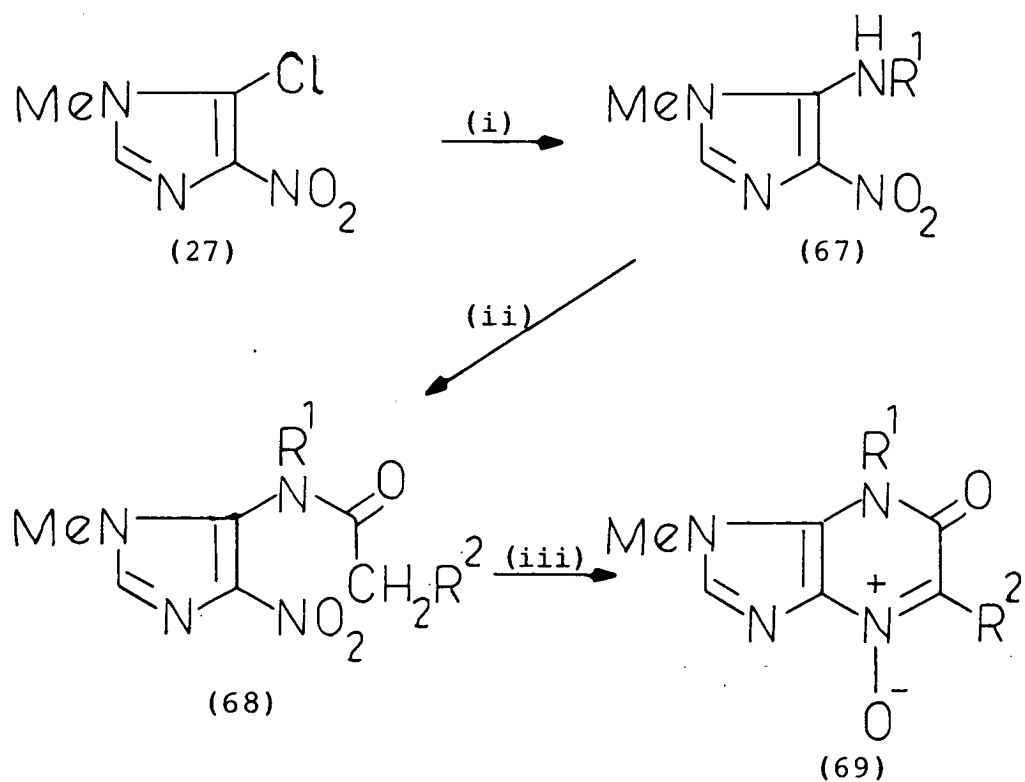
The base-catalysed cyclisation of α -substituted 2-nitroacetanilides to otherwise inaccessible quinoxalin-3(4H)-one 1-N-oxides can be achieved by a variety of basic catalysts and



(i) 4% NaOH aq. - pyridine, 24°, 1h.

(ii) 4% NaOH aq. - heat, 0.5h.

Scheme 19

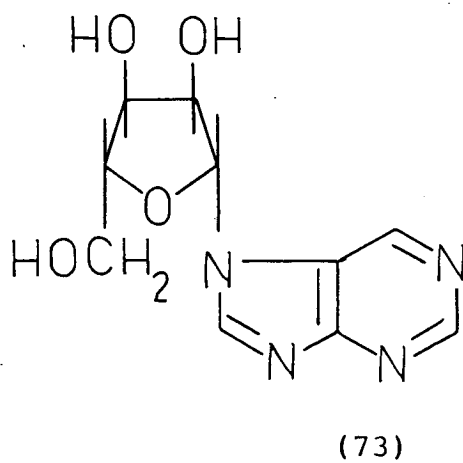
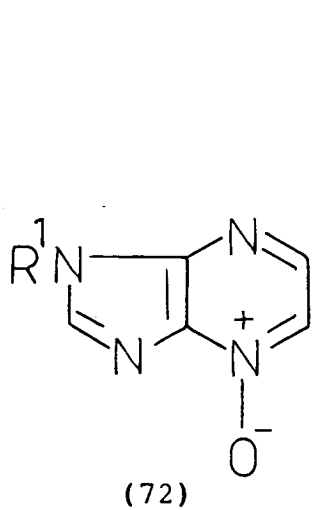
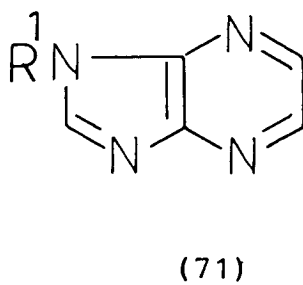
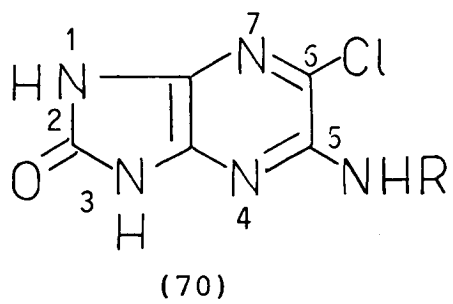


(i) R¹NH₂.

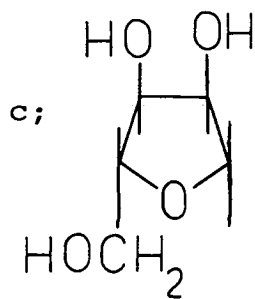
(ii) R²CH₂CCl.
 $\begin{array}{c} \text{O} \\ \parallel \\ \text{O} \end{array}$

(iii) base.

Scheme 20



R¹
 a; H
 b; Me

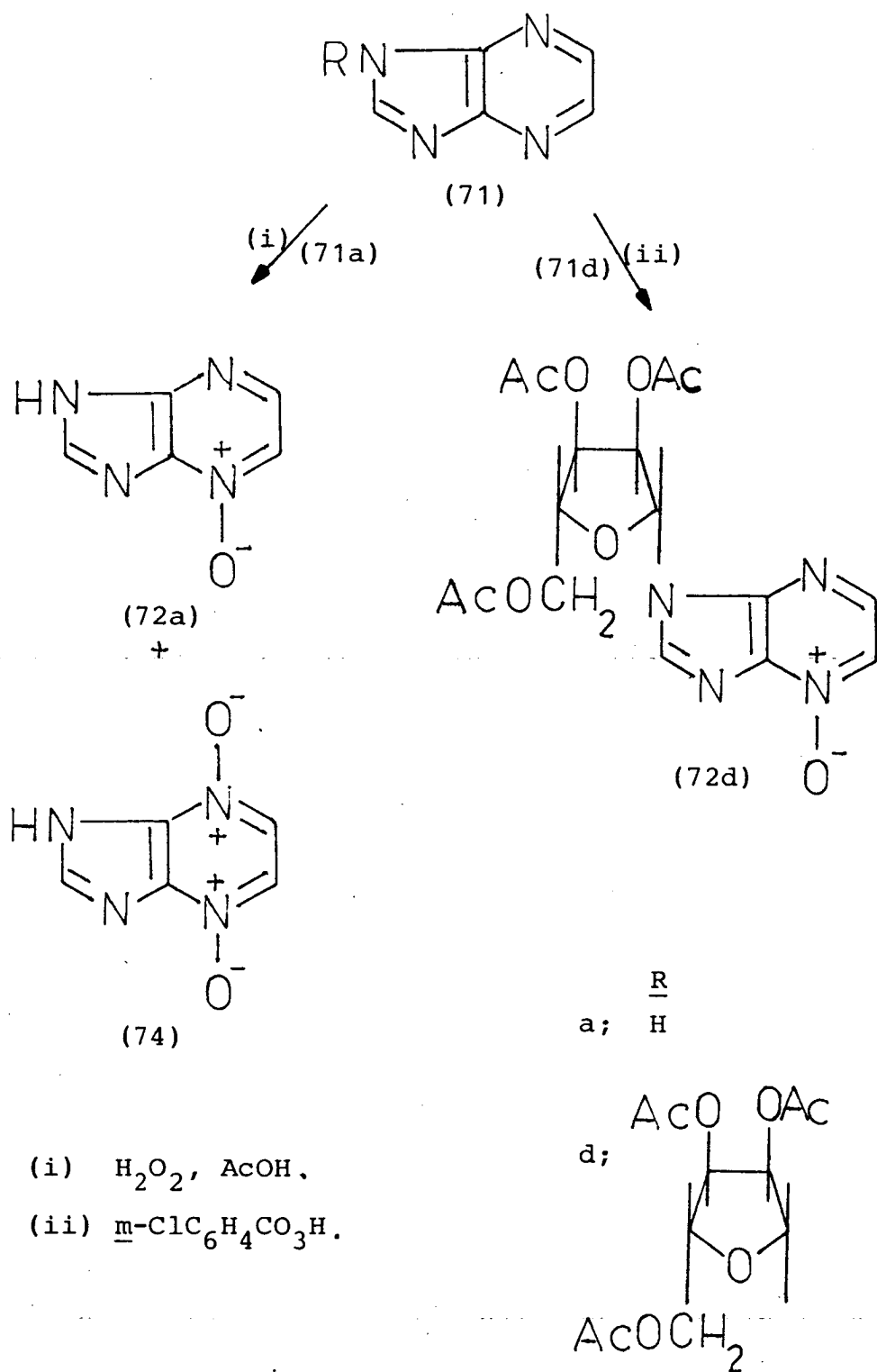


Scheme 21

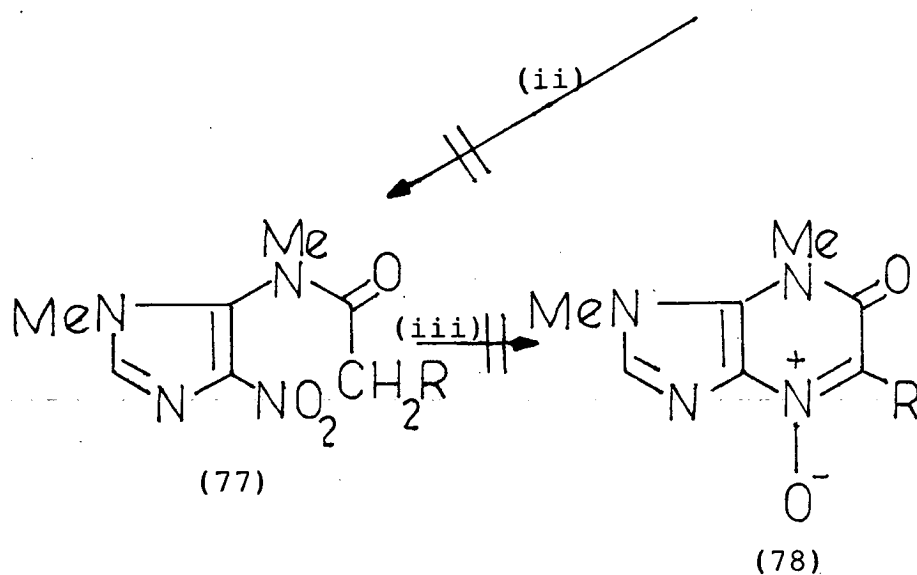
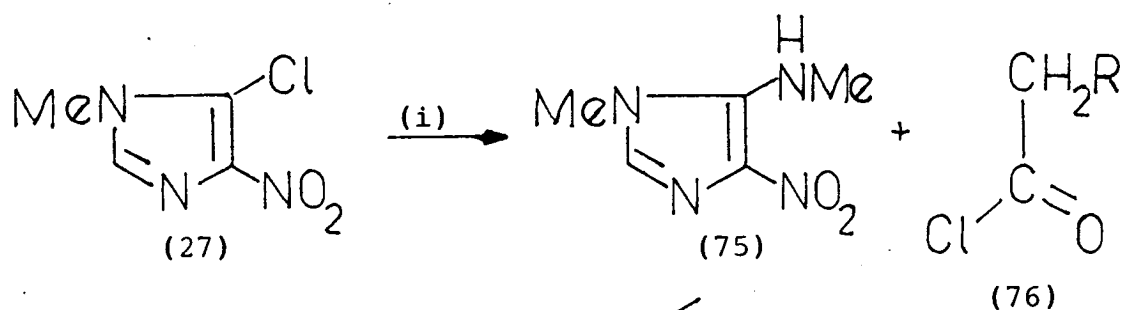
often under mild conditions. The only structural requirement for this type of cyclisation appears to be the activation of the methylene group in the acetanilide side-chain by an electron-withdrawing α -substituent. For example (Scheme 19) α -cyano-2-nitroacetanilide (64) can, under mildly basic conditions, undergo an aldol-type cyclisation to the quinoxalinone N-oxide (65).^{68,69} Stronger basic conditions result in the cyclisation of the anilide (64) to the 1-N-hydroxy-quinoxalin-2,3(1H,4H)-dione (66)⁶⁹ presumably via the hydrolysis of the cyano substituent in the cyanoquinoxalinone N-oxide (65).

The application of base-catalysed cyclisations of the types [(64)→(65) or (66)] to the corresponding imidazole derivatives (Scheme 20) would provide a useful general synthetic route to N-oxygenated imidazo[4,5-b]pyrazines (69). Thus, the nucleophilic displacement of the activated chlorine atom in the readily available⁶¹ chloro-nitro-imidazole (27) by ammonia and primary amines would provide a ready method for the synthesis of the ortho-amino-nitro-imidazoles (67), reaction of which with suitably functionalised acid chlorides would afford amides (68) which might be amenable to base-catalysed cyclisation to N-oxygenated imidazo[4,5-b]pyrazines (69). The latter are isosteric with N-oxygenated purines and are therefore of interest because of their potential biological activity.

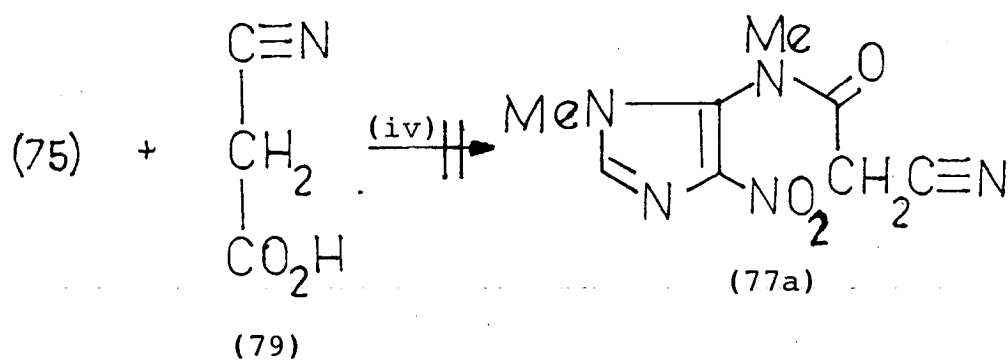
To date, the most interesting derivatives (Scheme 21) of the imidazo[4,5-b]pyrazine ring system from a biological point of view⁷⁰ are the 5-substituted amino-6-chloro-2-oxo compounds (70). These compounds are generally highly effective antihypertensive agents, active orally and possessing low mammalian toxicity. Various 1-substituted imidazo[4,5-b]-



Scheme 22



$\underline{\text{R}}$
 a; CN
 b; Ph



(i) MeNH_2 , EtOH.

(ii) $\text{MeO}(\text{CH}_2)_2\text{OMe}$, heat or heat (no solvent) or NaOAc, AcOH.

(iii) base.

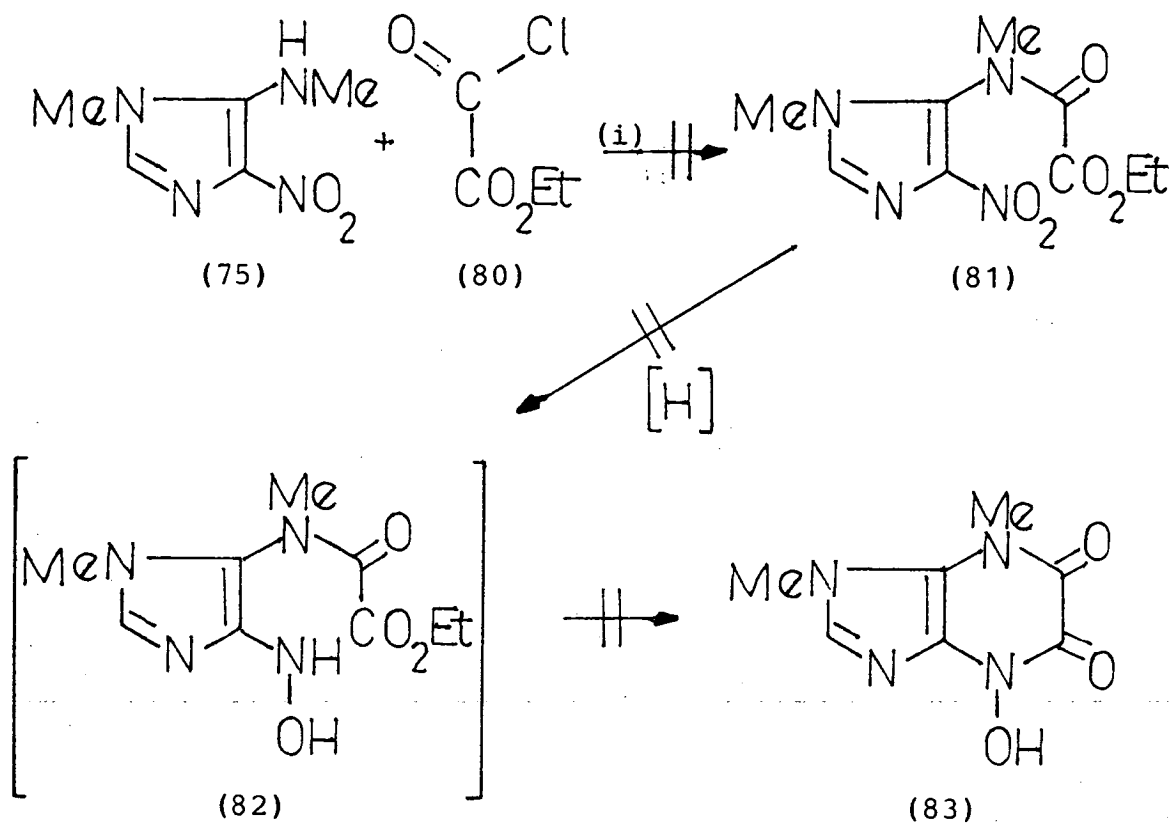
(iv) $\text{C}_6\text{H}_{11}\text{N}=\text{C}=\text{NC}_6\text{H}_{11}$, CH_2Cl_2 .

pyrazines (71) and their 4-N-oxides (72) have been examined⁷¹ as potential growth inhibitors of microbial and cancer cells. Only the imidazo[4,5-b]pyrazine 4-N-oxide (72a) and the 4-N-oxide (72c) of the nebularine analogue (71c) showed activity against *escherichia coli* and none of the derivatives affected the growth of cancer cells, despite the considerable activity of the purine, nebularine (73). The imidazo[4,5-b]pyrazine 4-N-oxide (72a) can be obtained⁷² by direct oxidation (Scheme 22) but the reaction is complicated by the co-formation in low yield of the 4,7-di-N-oxide (74). The peracid oxidation of the acetylated nucleoside analogue (71d) was demonstrated⁷² to afford the 4-N-oxide (72d) in reasonable yield.

The key starting-material for the proposed synthetic approach (Scheme 20) to N-oxygenated imidazo[4,5-b]pyrazines (69) was the readily available 5-chloro-1-N-methyl-4-nitro-imidazole (27),⁶¹ the synthesis of which has been described previously (see page 19 and Scheme 8). The reaction (Scheme 23) of this nitro-imidazole derivative (27) with ethanolic methylamine has been described by Schubert and Heydenhauss⁷³ and afforded a good yield of the methylamino-imidazole (75). This compound was chosen for subsequent conversion into amides (77) suitably functionalised for cyclisation to the required N-oxygenated imidazo[4,5-b]pyrazines (78), a group of compounds which would be expected to show greater reactivity towards acylation compared with the parent amino-imidazole [Scheme 20; (67; $R^1=H$)], due to the greater basicity of the methylamino-substituent in (75) compared with the amino-group in (67; $R^1=H$). In practice however, the attempted reaction of the methylamino-imidazole (75) with cyanoacetyl chloride (76a)

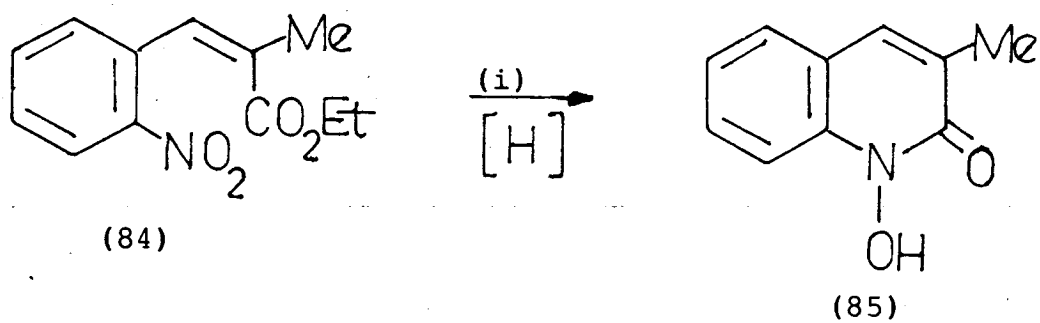
[readily prepared⁷⁴ from cyanoacetic acid (79)] afforded only an intractable gum together with a low recovery of the unreacted starting-material. Cyanoacetyl chloride is thermolabile and presumably decomposes under the reaction conditions employed before it can react with the methylamino-imidazole (75). In an alternative approach (Scheme 23) to the cyanoacetamido-imidazole (77a), the reaction of the methylamino-imidazole (75) with cyanoacetic acid (79) in the presence of the condensation catalyst,⁷⁵ dicyclohexylcarbodiimide (DCC), was investigated. However this attempt to synthesise the cyanoacetamido-imidazole (77a) gave only a mixture of the unreacted methylamino-imidazole (75) and N,N'-dicyclohexylurea, the hydration product of DCC. The lack of success in attempts to synthesise the cyanoacetamido-imidazole (77a) prevented the study of its base-catalysed cyclisation to the N-oxygenated imidazo[4,5-b]pyrazine (78a). The failure of the methylamino-imidazole (75) to react with cyanoacetyl chloride or with cyanoacetic acid in the presence of DCC can be attributed to steric hindrance by the methyl moiety of the methylamino-substituent, which would appear to override its expected enhanced reactivity towards acylation (see above). A further factor is the instability of cyanoacetyl chloride, which suffers thermal decomposition under the conditions of this attempted condensation with the methylamino-imidazole (75).

Having failed to obtain the cyanoacetamido-imidazole (77a) it was decided next to attempt the preparation (Scheme 23) of the phenylacetamido-imidazole (77b) by the reaction of the methylamino-imidazole (75) with the readily available phenylacetyl chloride (76b). Being relatively thermally stable it



(i) NaOAc, AcOH or pyridine.

Scheme 24

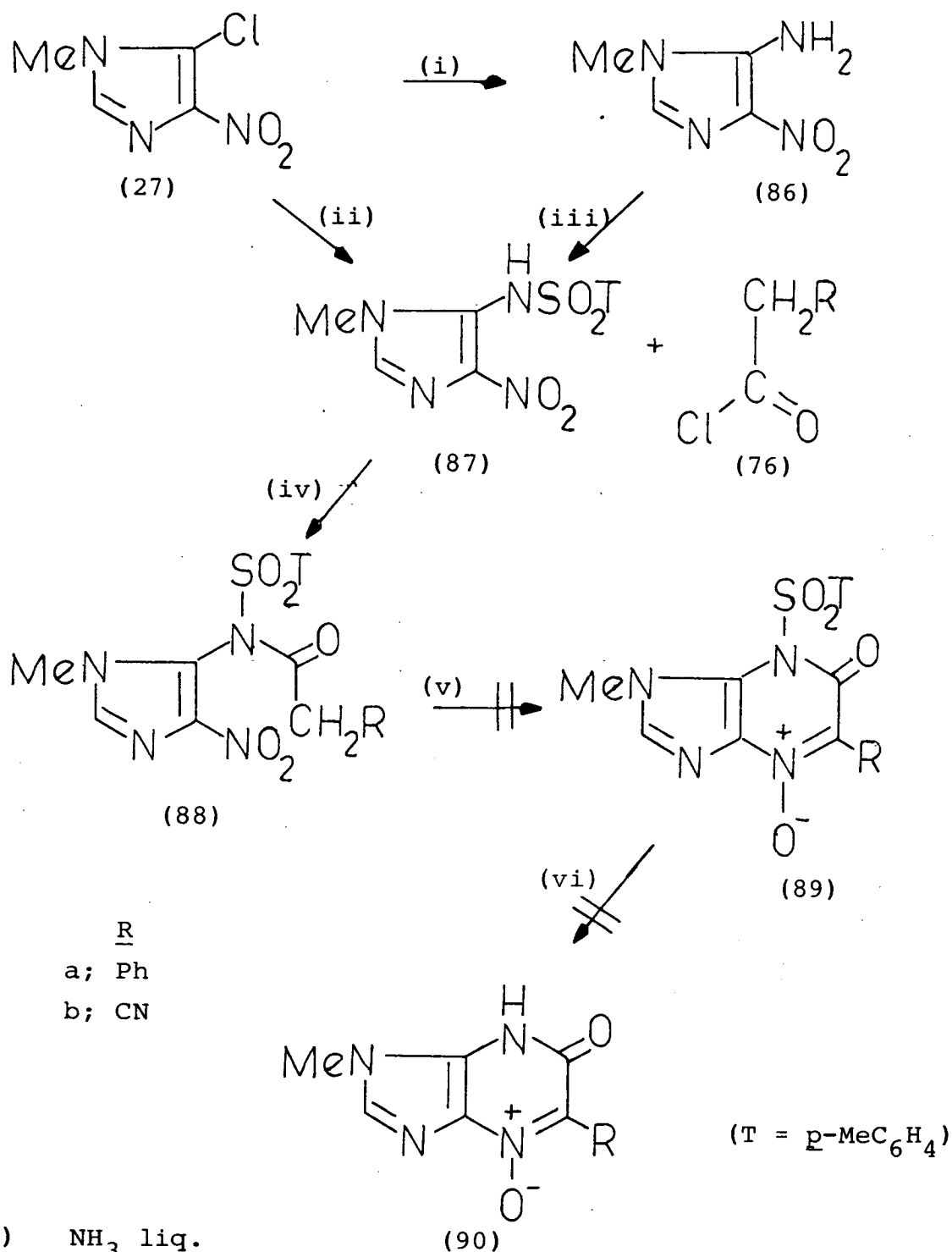


(i) $(\text{NH}_4)_2\text{S}$, EtOH.

Scheme 25

was anticipated that phenylacetyl chloride could, if necessary, be reacted with the methylamino-imidazole (75) under forcing conditions to afford the phenylacetamido-imidazole (77b), a compound which should be amenable to base-catalysed cyclisation to the corresponding N-oxygenated imidazo[4,5-b]pyrazine (78b). However, heating the methylamino-imidazole (75) with phenylacetyl chloride in the absence of solvent afforded on workup an intractable solid, shown by t.l.c. to be an unresolvable multicomponent mixture. Milder conditions also failed to afford the desired phenylacetamido-imidazole (77b). Thus reaction of the methylamino-imidazole (75) with phenylacetyl chloride (76b) in glacial acetic acid in the presence of sodium acetate afforded a good recovery of the unreacted starting-material (75) together with some phenylacetic acid. The failure of attempts to convert the methylamino-imidazole (75) into the phenylacetyl derivative (77b) further demonstrates the reluctance of the methylamino-substituent in the imidazole derivative (75) to undergo acylation and again precluded the proposed investigation of the base-catalysed cyclisation of the nitro-phenylacetamido-imidazole (77b) to the N-oxygenated imidazo[4,5-b]pyrazine (78b).

The failure of attempts (Scheme 23) to convert the methylamino-nitroimidazole (75) into acetamido derivatives (77a and b) suitable for base-catalysed cyclisation to N-oxygenated imidazo[4,5-b]pyrazines (78a and b) prompted an alternative synthetic approach (Scheme 24) to these polyazaheterocyclic compounds. This involved the condensation of the methylamino-imidazole (75) with ethoxalyl chloride (80) to afford the



(i) NH_3 liq.

(ii) TSO_2NH_2 , NaOEt , EtOH , heat, or NaH , DMF , heat.

(iii) TSO_2Cl , NaH , DMF .

(iv) NaOH , H_2O or NaH , DMF .

(v) base.

(vi) H^+ ; H_2O , heat.

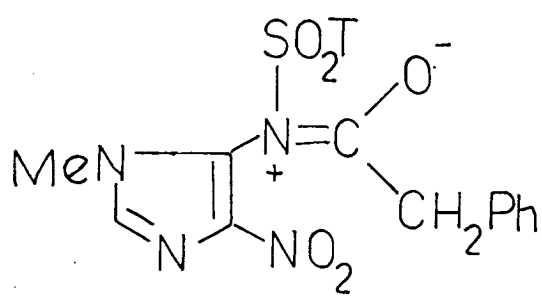
ethyl N-imidazolyloxamate (81), which it was hoped would undergo reductive cyclisation through the hydroxyamino-derivative (82) to afford the interesting imidazo[4,5-b]-pyrazine hydroxamic acid (83). Analogy for the reductive cyclisation step [(81)→(82)→(83)] in this synthetic scheme is provided by the reductive cyclisation with ammonium sulphide (Scheme 25) of the 2-nitrophenyl-methacrylate (84) to the N-hydroxyquinolin-2(1H)-one (85), reported⁷⁶ by Newbold and Spring et al. However, the attempted reaction of the methylamino-imidazole (75) with ethoxalyl chloride in acetic acid in the presence of sodium acetate afforded only a good recovery of the unreacted methylamino-imidazole (75). The attempted reaction of the latter with ethoxalyl chloride catalysed by pyridine likewise failed to afford the desired nitroimidazolyloxamate (81), only the unreacted starting-material (75) and an uncharacterisable gummy solid containing more unreacted starting-material (75) being obtained.

The apparent unsuitability of the methylamino-imidazole (75) as a starting-material for the synthesis of nitroimidazole derivatives [ie. (77a and b) and (81)] suitable for cyclisation to N-oxygenated imidazo[4,5-b]pyrazines [ie. (78a and b) and (83)] prompted the study (Scheme 26) of the tosyl derivative (87) as an alternative starting-material. It was hoped that the presence of the acidic tosylamino-substituent in the nitroimidazole derivative (87) would promote its base-catalysed reaction with suitable acid chlorides (76a and b) to afford α-substituted 2-nitroimidazolyl-acetamides (88). These compounds are set up for base-catalysed cyclisation to imidazo[4,5-b]pyrazine N-oxides (89), hydrolytic removal of

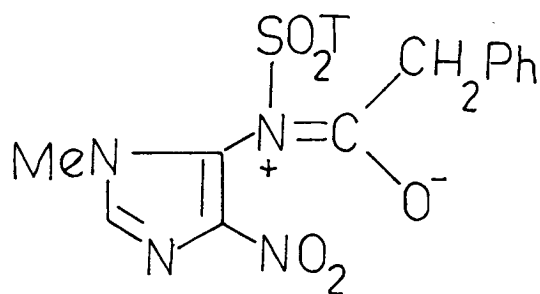
the N-tosyl substituent from which would yield the parent imidazo[4,5-b]pyrazine N-oxides (90). The synthesis of the tosylamino-imidazole (87) by the reaction of the chloro-nitroimidazole (27) with the sodium salt of toluene-p-sulphonamide has been reported⁷⁷ in the literature without experimental details. In the present studies the tosylamino-imidazole (87) was readily prepared by two alternative methods. In the first toluene-p-sulphonamide (tosylamide) was converted in ethanolic sodium ethoxide into the sodium salt, one equivalent of which was reacted in situ under reflux with the chloro-nitroimidazole (27) to afford the tosylamino-imidazole (87) in moderate yield together with unreacted tosylamide. The use of a two-fold excess of the sodium salt of tosylamide and prolonging the reaction time afforded a much improved yield of the tosylamino-imidazole (87). The latter compound was also formed in lower yield by reaction of the chloro-nitroimidazole (27) with the sodium salt of tosylamide prepared in situ from tosylamide and sodium hydride in dimethylformamide.

The alternative preparation of 1-N-methyl-4-nitro-5-tosylaminoimidazole (87) consisted of the conversion of 5-chloro-1-N-methyl-4-nitroimidazole (27) in liquid ammonia in high yield into the known⁷⁸ 5-amino-1-N-methyl-4-nitroimidazole (86). Reaction of the latter with sodium hydride in dimethylformamide followed by tosyl chloride afforded the tosylamino-imidazole (87) in moderate yield.

The reaction (Scheme 26) of the tosylamino-imidazole (87) with phenylacetyl chloride in the presence of aqueous sodium hydroxide afforded a low yield of a colourless product which

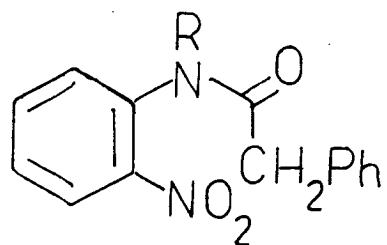


(88a) (A)

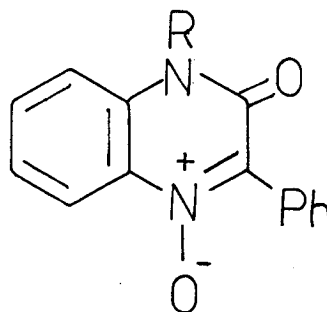
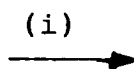


(88a) (B)

Scheme 27



(91)



(92)

R

a; H

b; Me

(i) 20% KOH aq, pyridine, 100°, 1h.

Scheme 28

gave analytical and mass spectral data consistent with the expected N-phenylacetyl-N-toluene-p-sulphonylamino-imidazole structure (88a). The spectroscopic properties of the product were also consistent with the proposed structure (88a). Thus, its i.r. spectrum showed amide carbonyl absorption at 1740 cm^{-1} and bands at 1510 and 1350 cm^{-1} due to a nitro group. The ^1H n.m.r. spectrum of the product was also entirely consistent with the proposed structure (88a), the only unusual feature being the presence of two singlets at $\delta 3.64$ and 3.62 which can be assigned to the methylene protons of the phenylacetyl substituent. This feature can be explained (Scheme 27) by the existence of the phenylacetamido-imidazole (88a) in two discrete conformations (A) and (B) resulting from hindered rotation about the amide $\text{N}-\text{C}=\text{O}$ bond. An alternative explanation for the appearance of the ^1H n.m.r. absorption of the methylene protons in the amide (88a) is that they are diastereotopic and thus magnetically non equivalent. The expected pattern for the ^1H n.m.r. resonance absorption of diastereotopic protons is a doublet of doublets rather than the two discrete one proton singlets actually observed. However, the coupling between the geminal diastereotopic methylene protons of the amide (88a) may be too small to be observable in its ^1H n.m.r. spectrum. The nitro-phenylacetamido-imidazole (88a) was obtained in substantially improved yield by converting the tosylamino-imidazole (87) into its sodium salt with sodium hydride in dimethylformamide followed by reaction with the acid chloride.

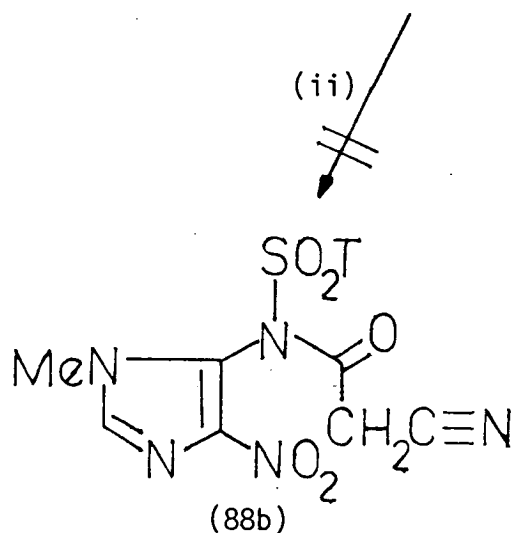
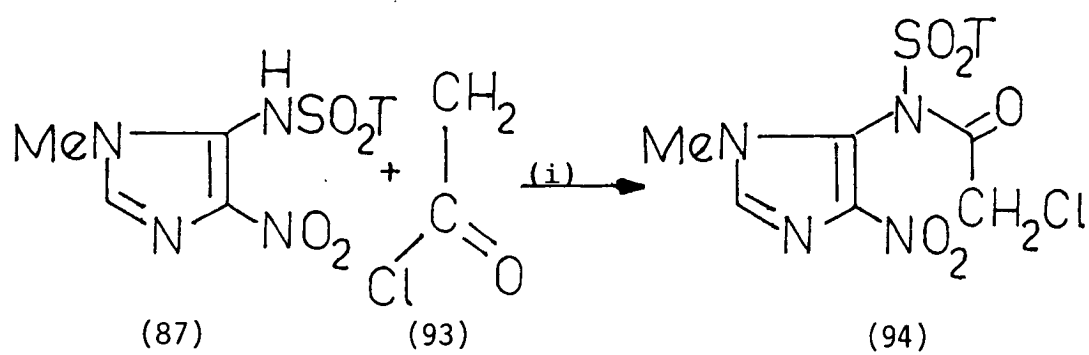
The expected product (Scheme 26) of the base-catalysed cyclisation of the nitro-phenylacetamido-imidazole (88a) was the N-tosyl-imidazo[4,5-b]pyrazinone N-oxide (89a) which should

be converted, in turn, by hydrolysis, into the parent imidazo[4,5-b]pyrazinone N-oxide (90a). This proposed base-catalysed cyclisation of the N-tosyl-ortho-nitro-phenyl-acetamido-imidazole (88a) to the N-oxygenated imidazo[4,5-b]pyrazine (89a) is analogous to the known⁴³ base-catalysed cyclisation (Scheme 28) of α -aryl-ortho-nitroacetanilides to 3-arylquinoxalin-2(1H)-one N-oxides, which despite the weakly acidic nature of the methylene centre in the side-chain of the former, proceeds in good yield. Cyclisations of this type (Scheme 28) are exemplified by the formation⁷⁹ of the quinoxalinone N-oxide (92a) in good yield by treatment of α -phenyl-2-nitroacetanilide (91a) with aqueous potassium hydroxide in pyridine. However the use of ethanolic sodium ethoxide as the cyclisation catalyst in the latter reaction gives only a low yield of the N-oxide (92a) due to competing solvolysis of the amide side-chain in the nitroacetanilide derivative (91a).⁶⁹ In contrast, the N-methyl- α -phenyl-ortho-nitroacetanilide (91b) undergoes⁶⁹ cyclisation in high yield to the quinoxalinone N-oxide (92b) on treatment with ethanolic sodium ethoxide.

In practice, the attempted base-catalysed cyclisation of the N-tosyl-ortho-nitro-phenylacetamido-imidazole (88a) failed to afford the expected N-oxygenated imidazo[4,5-b]pyrazine (89a). Thus, treatment of the imidazole derivative (88a) with aqueous potassium hydroxide in pyridine gave only the tosylamino-imidazole (87), produced by hydrolysis, together with small amounts of tosylamide and phenylacetic acid. Similarly heating the nitro-phenylacetamido-imidazole (88a) with triethylamine in ethanol gave only the amino-nitro-imidazole (86), produced by hydrolysis, and an intractable oil.

Since the failure of the nitro-phenylacetamido-imidazole (88a) to undergo base-catalysed cyclisation could be attributed to the low reactivity (i.e. acidity) of the methylene centre in the phenylacetamido side-chain, hence allowing side-chain hydrolysis to compete with the cyclisation, attention was next turned to the synthesis and base-catalysed cyclisation of the nitro-cyanoacetamido-imidazole (88b). It was hoped that the greater acidity of the methylene centre in the cyanoacetamide derivative (88b) would promote its base-catalysed cyclisation to the imidazo-pyrazine N-oxide (89b). The base-catalysed cyclisation (Scheme 19) of α -cyano-2-nitroacetanilides [e.g. (64)] to 3-cyanoquinoxalin-2(1H)-one N-oxides [e.g. (65)] is a well-documented^{68,69} reaction.

Reaction of the sodium salt of the nitro-tosylamino-imidazole (87) with cyanoacetyl chloride (76b) afforded a good yield of a solid product whose properties are in accord with its formulation as the nitro-cyanoacetamido-imidazole (88b). Its i.r. spectrum showed carbonyl absorption at 1755 cm^{-1} and absorption at 1510 and 1345 cm^{-1} due to a nitro-group. The product's ^1H n.m.r. spectrum was also consistent with the nitro-cyanoacetamido-imidazole structure (88b), the only unusual feature being the absorption of the methylene protons as two discrete one proton singlets at $\delta 3.44$ and 3.24 rather than as the expected lone two proton singlet. The same absorption pattern was also observed for the methylene protons of the nitro-phenylacetamido-imidazole (88a). As in this case the ^1H n.m.r. absorption of the methylene protons of the cyanoacetoamido derivative (88b) can be attributed to its

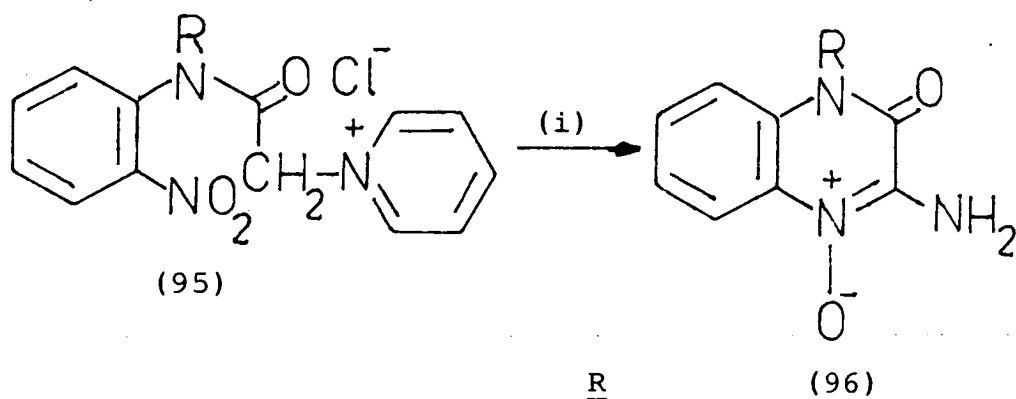


(i) NaH, DMF,

(ii) KCN.

(T = p-MeC₆H₄)

Scheme 29



R

a; H

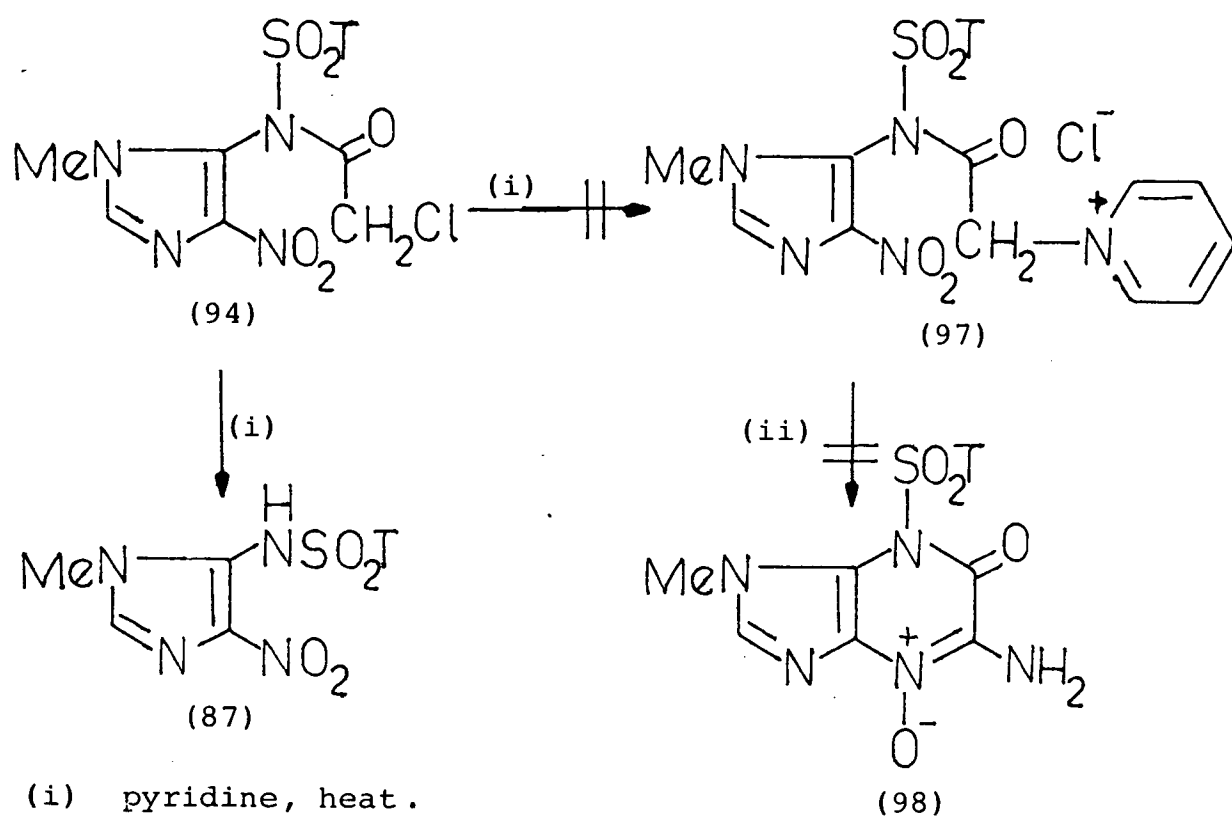
b; Me

(i) piperidine, MeOH, heat, 3h.

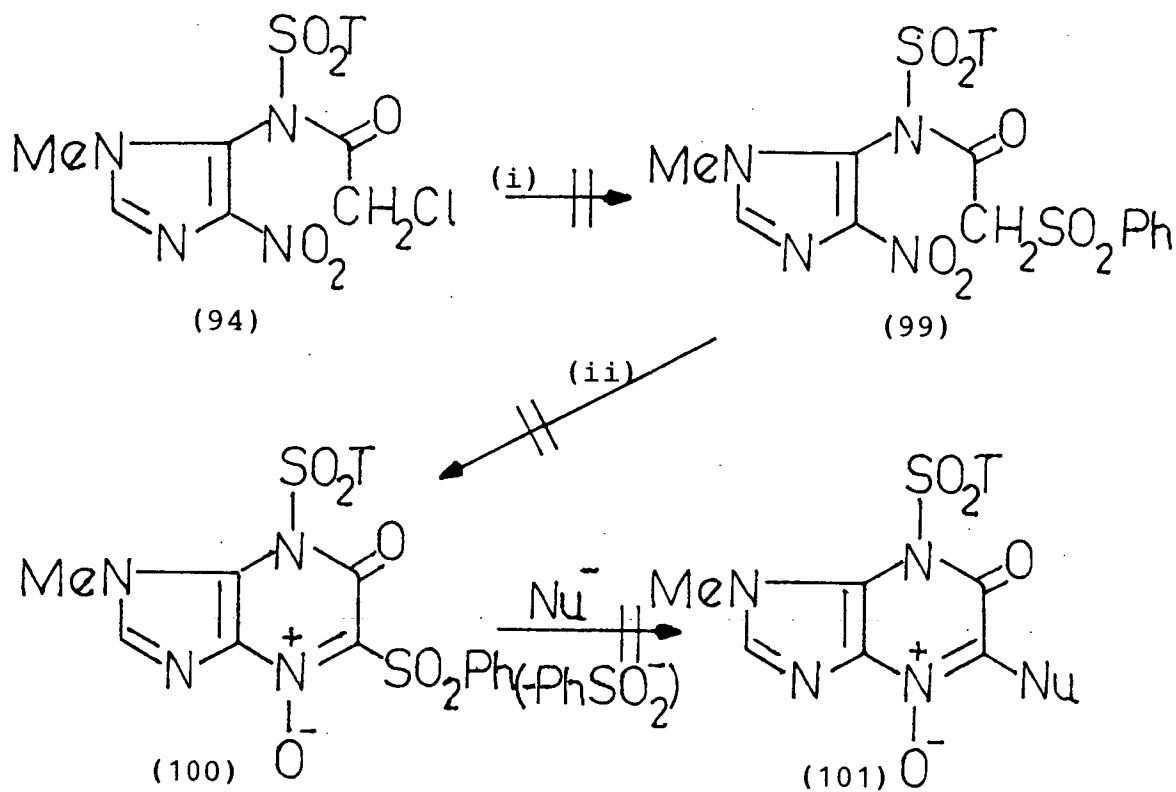
Scheme 30

existence in two predominant conformations due to hindered rotation about the N-C=O bond (see Scheme 27) or to the diastereotopic character of the methylene protons associated with a low geminal H-H coupling constant (see above). The attempted purification of the nitro-cyanoacetamido-imidazole (88b) by crystallisation resulted in its thermal or solvolytic decomposition to the tosylamino-imidazole (87). This thermal instability of the nitro-cyanoacetamido-imidazole (88b) precluded its combustion analysis. Moreover, the same fragmentation to the tosylamino-imidazole (87) and presumably cyanoketene ($\text{NCCH}=\text{C}=\text{O}$) is observed under electron impact. Thus, the mass-spectrum of the cyanoacetamido-imidazole (88b) fails to exhibit a molecular ion peak at m/e 363 but contains instead a peak of highest mass at m/e 296 corresponding to the tosylamino-imidazole (87) together with a peak at m/e 67 attributable to cyanoketene.

In order to obtain further evidence for the structure of the nitro-cyanoacetamido-imidazole (88b) it was decided to attempt its synthesis by another unambiguous route (Scheme 29). To this end the sodium salt of the tosylamino-imidazole (87) was prepared in situ by reaction with sodium hydride in dimethylformamide, and reacted with chloroacetyl chloride (93) to afford a high yield of a product whose analytical and spectroscopic properties were fully in accord with the expected nitro-chloroacetamido-imidazole structure (94). The intention (Scheme 29) was to react this chloroacetamido derivative (94) with potassium cyanide, thus providing an alternative route to the nitro-cyanoacetamido-imidazole (88b). In practice



Scheme 31

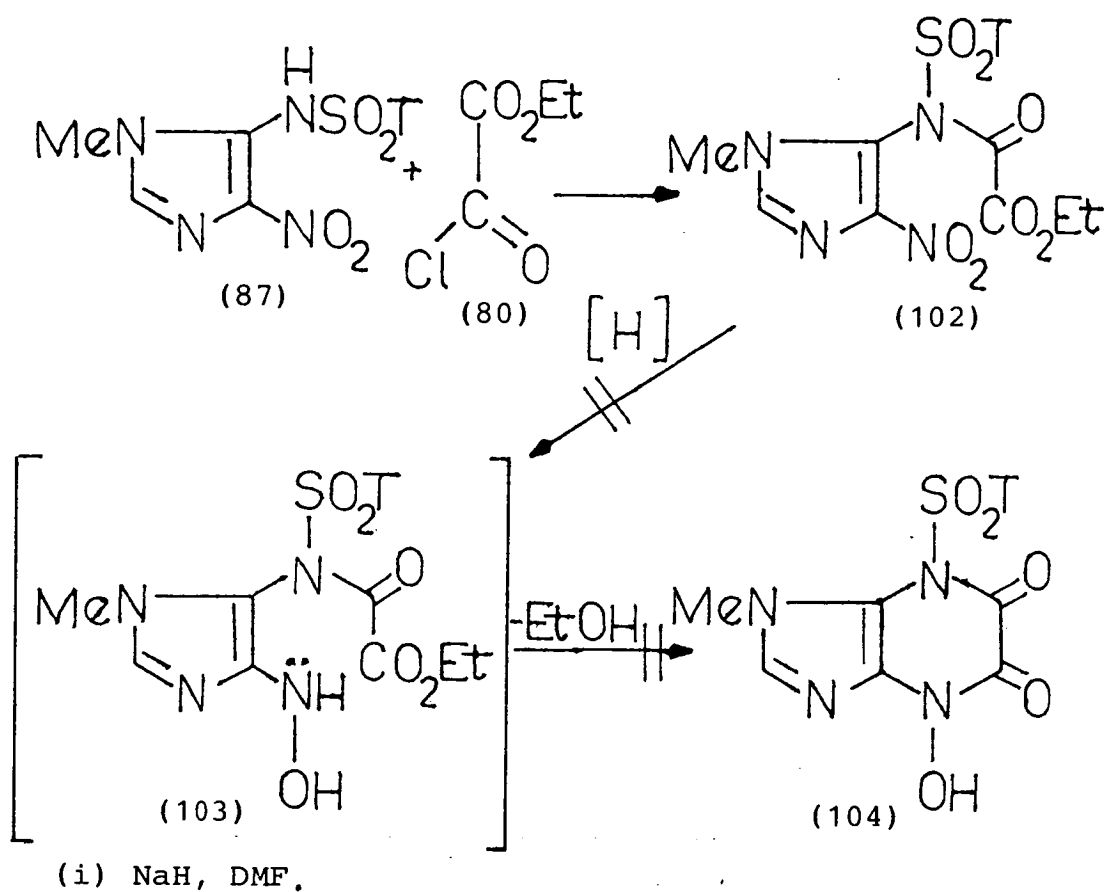


Scheme 32

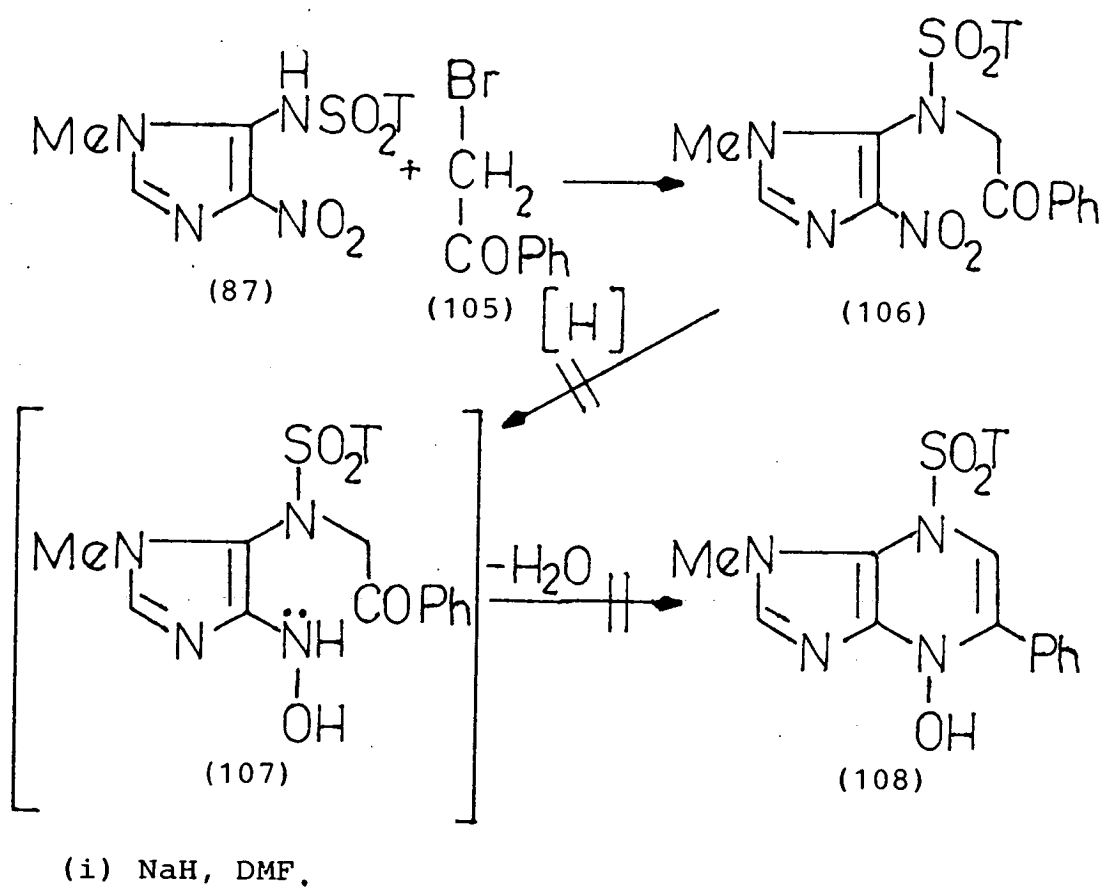
reaction of the chloroacetamide derivative (94) with potassium cyanide in aqueous ethanol resulted in its hydrolysis to the tosylamino-imidazole (87), again demonstrating the lability of the amide bond in N-tosyl-5-acetamido-imidazole derivatives such as (94) and (88b).

It has been demonstrated (Scheme 30)^{69,80} that pyridinium salts of the type (95) are cyclised in moderate yield to amino-quinoxalinone N-oxides (96) on treatment with methanolic piperidine. This nitro-group cyclisation occurs with concurrent solvolytic degradation of the pyridinium ring from which the amino-substituent is derived. It was therefore of interest to attempt the conversion (Scheme 31) of the chloroacetamido-imidazole (94) into the pyridinium salt (97) which in turn might undergo piperidine-catalysed cyclisation to the amino-imidazo-pyrazine N-oxide (98) in an analogous manner to the pyridinium salt (95). However, reaction of the chloroacetamido-imidazole (94) with pyridine resulted in hydrolysis to the tosylamino-imidazole (87) rather than formation of the pyridinium salt (97). This again illustrates the sensitivity of the amide bond in N-tosylacetamido-imidazoles such as (94) to hydrolysis, and precluded the investigation of the cyclisation of the pyridinium salt (97) to the imidazo[4,5-b]pyrazine N-oxide (98).

In a further attempt (Scheme 32) to exploit the N-tosyl-chloroacetamido-imidazole (94) for the synthesis of imidazo[4,5-b]pyrazine N-oxides it was decided to investigate its reaction with sodium benzenesulphinate which might afford the N-tosylbenzenesulphonylacetamido-imidazole (99). The formation of sulphones by the reaction of active halogen compounds



Scheme 33



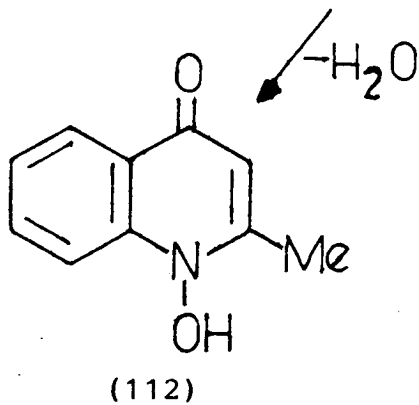
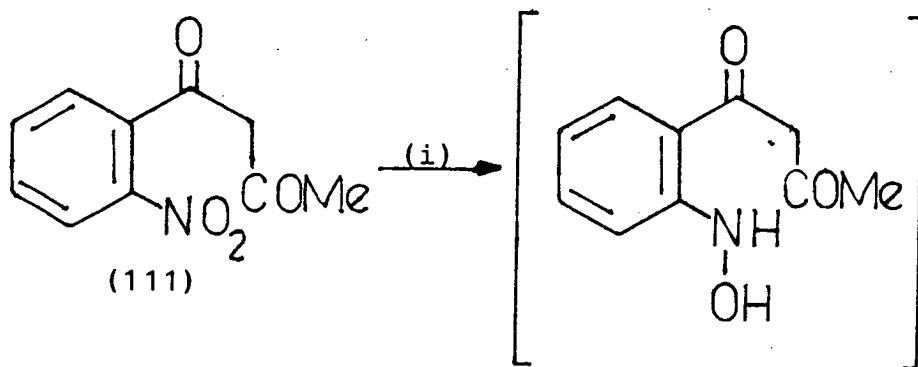
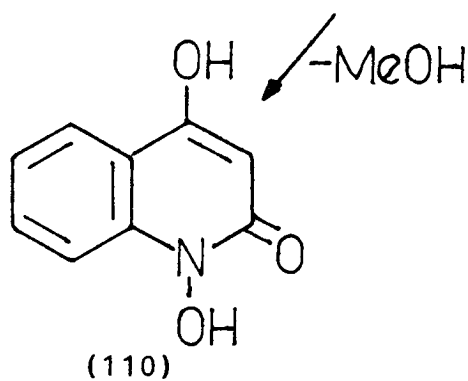
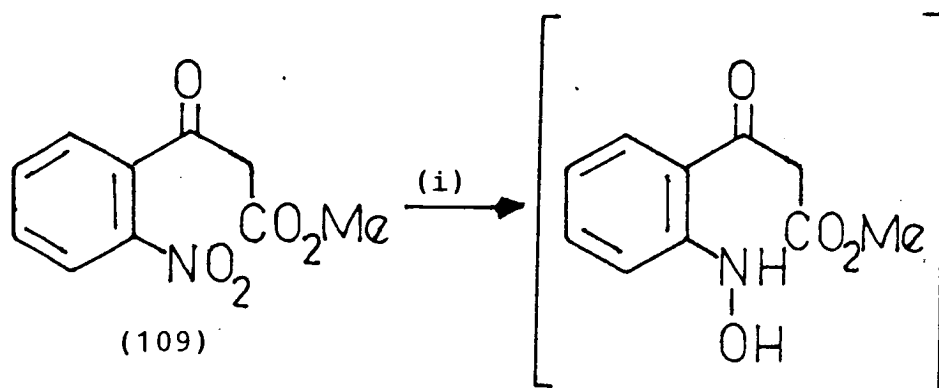
Scheme 34

with sodium benzenesulphinate is a well known process.⁸¹ The highly reactive methylene centre in the acetamido side-chain of the benzenesulphonyl-imidazole derivative (99) should promote its base-catalysed cyclisation to the benzenesulphonyl-imidazo[4,5-b]pyrazine N-oxide (100). The benzenesulphonyl substituent in this compound should be readily replaceable by a variety of nucleophiles, making it a useful intermediate for the synthesis of variously functionalised imidazo[4,5-b]pyrazine N-oxides (101). The reaction of the chloroacetamido-imidazole (94) with sodium benzenesulphinate in ethanol did not however afford the desired sulphone (99), the only products isolated being the tosylamino-imidazole (87) and a multi-component oil. The sensitivity of the amide side-chain once again precluded the further study of the synthetic approach to imidazo[4,5-b]pyrazine N-oxides outlined in Scheme 32.

The synthesis (Scheme 25) of 1-hydroxy-3-methylquinolin-2(1H)-one (85) by the reductive cyclisation of the nitrophenyl-methacrylate (84) has been described previously (see page 38). Cyclisations of this type involve the in situ reductive formation and cyclisation of hydroxyamino intermediates, and having failed to achieve the projected base-catalysed cyclisation of suitable nitroimidazoles to imidazo[4,5-b]pyrazine N-oxides it was decided to investigate synthetic methods for the latter based on reductive cyclisation. To this end (Scheme 33) the synthesis of the N-ethoxalyl-N-tosylamino-imidazole (102) was attempted, in the anticipation that it would undergo reductive cyclisation through the hydroxyamino-intermediate (103) to afford the previously unknown N-hydroxy-imidazo[4,5-b]pyrazinedione (104). Conversion of the tosyl-

amino-imidazole (87) into its sodium salt by reaction with sodium hydride, followed by reaction with ethoxalyl chloride (80), gave a moderate yield of a colourless crystalline product which gave analytical and mass spectral data consistent with the expected ethoxalylamino-imidazole structure (102). The spectroscopic properties of the product were also in accord with this structure. Its i.r. spectrum showed broad carbonyl absorption at $1750-1720\text{ cm}^{-1}$ as well as bands at 1510 and 1300 cm^{-1} due to a nitro-group. The ^1H n.m.r. spectrum showed proton resonances due to the p-tolyl and ethoxycarbonyl substituents as well as the usual one- and three-proton singlets at $\delta 8.2$ and 3.8 due to the imidazole ring CH and N-methyl substituents respectively.

Disappointingly the attempted reductive cyclisation of the ethoxalylamino-imidazole (102) did not afford the desired N-oxygenated imidazo[4,5-b]pyrazine (104). Thus catalytic hydrogenation over 10% palladium-on-charcoal failed to result in any hydrogen uptake and on workup the only materials isolated were the tosylamino-imidazole (87) and unresolvable multi-component gums. Similarly the attempted reductive cyclisation of the ethoxalylamino-imidazole (102) to the N-hydroxy compound (104) in alkaline solution using sodium borohydride in the presence of 10% palladium-on-charcoal, under conditions known⁸² to effect such reductive cyclisations, afforded only the scission product 1-N-methyl-4-nitro-5-toluene-p-sulphonylamino-imidazole (87) and not the hoped for N-hydroxy-imidazo-pyrazinedione (104). The cleavage of the ethoxalylamino-imidazole (102) to the tosylamino-imidazole (87) under reductive conditions again demonstrates the lability of the amide linkage in N-

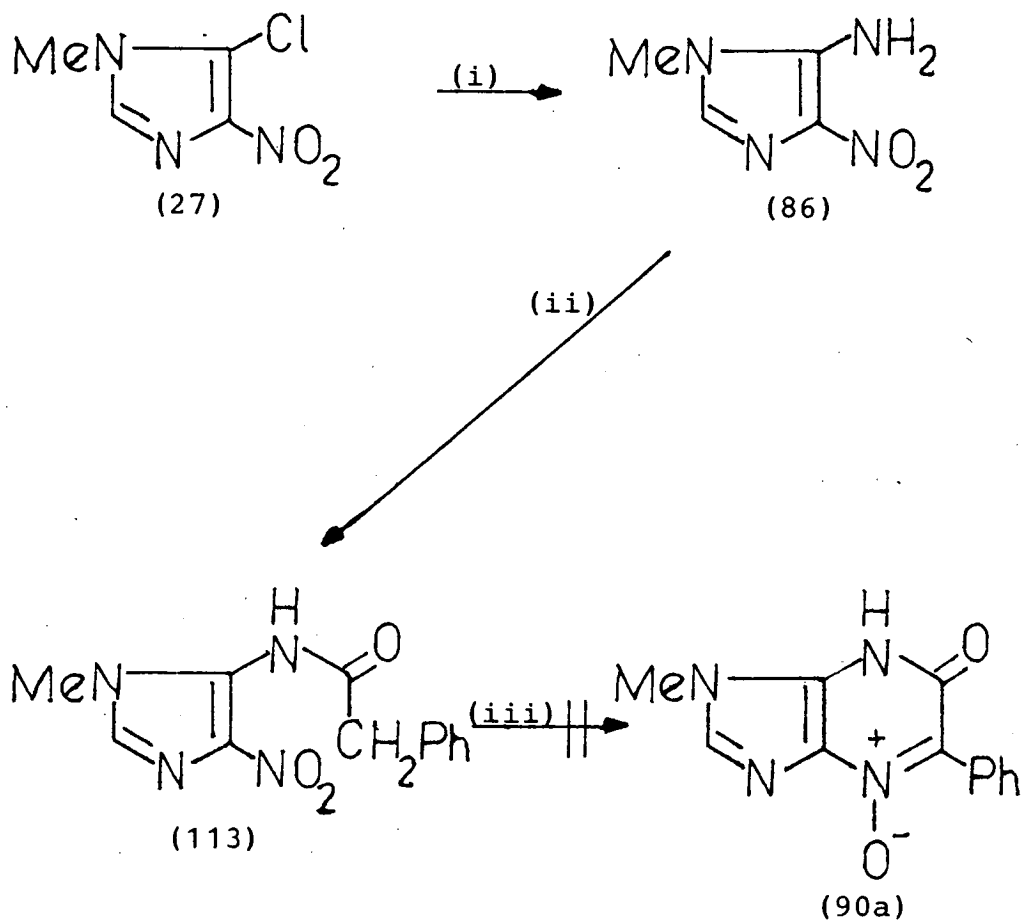


(i) NaBH_4 , Pd-C, NaOH, MeOH, H_2O .

tosylacylamino-imidazoles [e.g. (102)] under a variety of reaction conditions.

Having failed to achieve the reductive cyclisation of the ethoxalylamino-imidazole (102) to the N-hydroxy-imidazopyrazinedione (104) attention was next turned to the synthesis (Scheme 34) of the N-phenacyl-N-tosylamino-imidazole (106). This compound lacks the labile amide link present in the ethoxalylamino-imidazole (102) and might therefore undergo reductive cyclisation (Scheme 34) through the intermediacy of the hydroxyamino-imidazole (107) to afford the N-hydroxy-imidazo[4,5-b]pyrazine derivative (108). The proposed reductive cyclisation [(106)→(107)→(108)] is analogous to the reductive synthesis of N-hydroxyquinolines described by Coutts and Wibberley.⁸² These authors showed (Scheme 35) that the reductive cyclisation of methyl 2-nitrobenzoylacetate (109) and 2-nitrobenzoylacetone (111) using sodium borohydride in the presence of 10% palladium-on-charcoal affords 1,4-dihydroxyquinolin-2(1H)-one (110) and 1-hydroxy-2-methylquinolin-4(1H)-one (112) respectively, through the intermediacy of the corresponding 2-hydroxyamino-derivatives.

The N-phenacyl-N-tosylamino-imidazole (106) was readily prepared (Scheme 34) by the reaction of the tosylamino-imidazole (87) with sodium hydride followed by reaction of the resulting sodium salt with 2-bromoacetophenone (105). The N-phenacyl-N-tosylamino-imidazole (106) gave analytical and mass spectral data consistent with the assigned structure, which was further confirmed by the compound's spectroscopic properties. Its i.r. spectrum showed carbonyl absorption at 1705 cm^{-1} and bands due to a nitro group at 1505 and 1340 cm^{-1} . The ^1H n.m.r. spectrum



(i) NH_3 liq.

(ii) NaH , DMF , PhCH_2COCl .

(iii) KOH , H_2O , pyridine, 100° , 1h.

Scheme 36

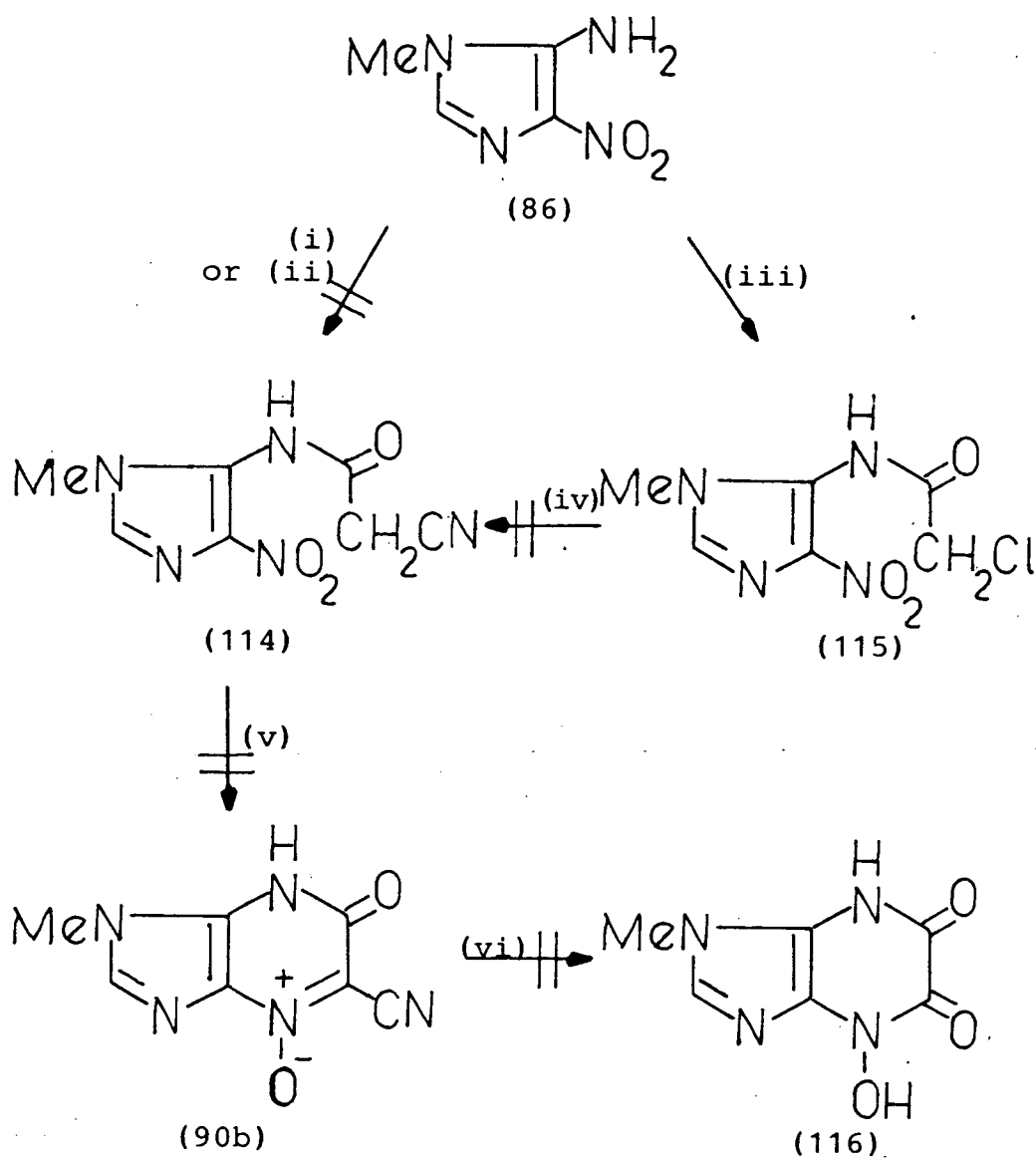
of the N-phenacyl-N-tosylaminoimidazole (106) showed the expected three-proton singlets at δ 3.98 and 2.40 due to the imidazole and tosyl methyl substituents respectively. The methylene protons of the compound (106) absorbed as two doublets centered at δ 5.58 and 5.05. This multiplicity can be attributed to the magnetic non-equivalence of the methylene protons as a result of hindered rotation about the N-CH₂ bond in the phenacyl derivative (106).

Unfortunately the attempted reductive cyclisation of the N-phenacyl-N-tosylamino-imidazole (106) did not afford the expected N-hydroxyimidazopyrazine (108). Thus the attempted catalytic hydrogenation of the N-phenacyl-N-tosylamino-imidazole (106) gave only an intractable oil whose t.l.c. showed it to be an unresolvable multicomponent mixture from which no identifiable material could be obtained.

The foregoing studies clearly demonstrate that though nitro-imidazole derivatives with ortho-tosylamino side-chains suitably functionalised for base-catalysed or reductive cyclisation to N-oxygenated imidazo[4,5-b]pyrazines, are readily synthesised, such compounds tend to undergo side-chain scission rather than cyclisation. The tendency for ortho-nitro N-substituted N-tosylamino-imidazoles to undergo side-chain scission can be attributed to the stability of the 1-N-methyl-4-nitro-5-tosylamino-imidazole anion as a leaving-group and it was therefore of interest to investigate the synthesis and cyclisation of analogous ortho-nitro N-substituted amino-imidazoles lacking the N-tosyl substituent. The obvious starting-material for such imidazole derivatives (Scheme 36) is 5-amino-1-N-methyl-4-nitroimidazole (86)⁷⁸ which was readily

prepared by the reaction of the known⁶¹ compound, 5-chloro-1-N-methyl-4-nitroimidazole (27), with ammonia under pressure as discussed previously. Because of the expected low nucleophilicity of the amino-substituent in the amino-nitro-imidazole (86) it was anticipated that it would not undergo direct acylation to give the N-substituted ortho-amino-nitro-imidazoles required for cyclisation studies and that formation of the latter would require the initial conversion of the amino-nitro-imidazole (86) into its sodium salt. In practice, treatment of the amino-nitro-imidazole (86) with sodium hydride in dimethylformamide followed by phenylacetyl chloride (Scheme 36) afforded, together with some unreacted starting-material (86), a good yield of a yellow product which gave analytical and mass spectral data consistent with the α -phenylacetamido-imidazole structure (113). In further accord with this structure the compound showed i.r. carbonyl and nitro absorption at 1680, and 1500 and 1340 cm^{-1} respectively and its ^1H n.m.r. spectrum showed one-proton, two-proton, and three-proton singlets at δ 7.75, 3.54 and 3.76 due to the protons of the imidazole ring, the side-chain methylene substituent and the imidazole N-methyl groups respectively as well as a one-proton singlet at δ 10.65 attributable to the side-chain NH-group.

As already discussed (see Scheme 28) Ahmad and his co-workers⁷⁹ have demonstrated that heating α -phenyl-2-nitroacetanilide (91a) with aqueous potassium hydroxide in pyridine resulted in its cyclisation in good yield to the quinoxalinone N-oxide (92a), and it was anticipated that the nitroimidazole derivative (113) would undergo analogous cyclisation to the



(i) $\text{ClC(=O)CH}_2\text{CN}$, NaH.

(ii) $\text{HO}_2\text{CCH}_2\text{CN}$, $\text{C}_6\text{H}_{11}\text{N}=\text{C}=\text{NC}_6\text{H}_{11}$.

(iii) $\text{ClC(=O)CH}_2\text{Cl}$, NaH.

(iv) KCN.

(v) base.

(vi) H_2O .

Scheme 37

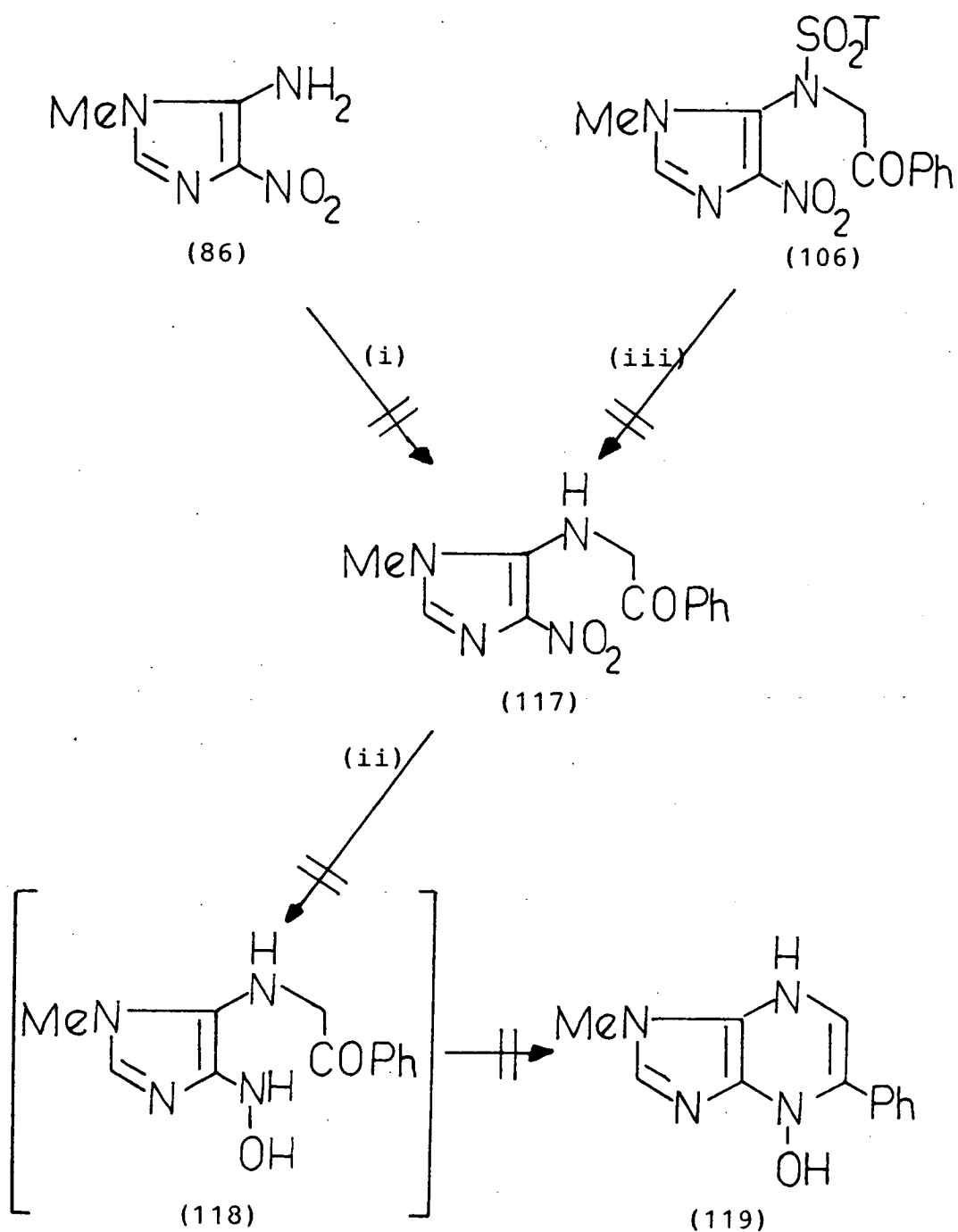
imidazo[4,5-b]pyrazinone N-oxide (90a). However, stirring the nitro-α-phenylacetamido-imidazole (113) with 20% w/v aqueous potassium hydroxide in pyridine at 100° afforded only a moderate recovery of the unreacted starting-material (113) and an intractable red oil rather than the desired imidazo[4,5-b]pyrazinone N-oxide (90a). This result can be attributed to the decomposition of the imidazole derivative (113) under the strongly basic conditions necessary to achieve its cyclisation as a consequence of the low methylene reactivity of the phenylacetamido side-chain. It was therefore decided to investigate (Scheme 37) the synthesis and base-catalysed cyclisation of 5-(α-cyanoacetamido)-1-N-methyl-4-nitroimidazole (114) which, having a more reactive side-chain methylene substituent, might undergo cyclisation under relatively mild basic conditions without the destruction of the imidazole nucleus which would account for the result observed with the α-phenylacetamido-imidazole (113). It has been shown (see Scheme 19) that α-cyano-2-nitroacetanilide (64) cyclises under relatively mildly basic conditions^{68,69} to afford the cyano-quinoxalenone N-oxide (65) in high yield, whereas using stronger basic conditions the product is the cyclic hydroxamic acid (66).⁶⁹ By analogy base-catalysed cyclisation of the cyanoacetamido-nitro-imidazole (114) should afford the imidazopyrazinone N-oxide (90b) and/or the N-hydroxyimidazopyrazine-dione (116).

The attempted reaction of the amine (86) with the readily available⁷⁴ cyanoacetyl chloride however, afforded only a high recovery of the starting amine (86) rather than the required

amide (114). The failure of this acylation reaction may be due to a combination of the relatively low basicity of the amino-substituent in the amino-imidazole (86), and hence low reactivity, coupled with the known⁷⁴ instability of cyanoacetyl chloride. The alternative synthetic approach to the cyanoacetamido-nitro-imidazole (114) involving the reaction of the amino-nitro-imidazole (86) with cyanoacetic acid in the presence of the condensation catalyst⁷⁵ dicyclohexylcarbodiimide was also unsuccessful. The unreacted amine (86) being recovered in quantitative yield together with dicyclohexylurea.

Having failed to synthesise the required cyanoacetamido-nitro-imidazole (114) by direct acylation of the amino-nitro-imidazole (86) it was next decided to attempt its indirect synthesis (Scheme 37) by conversion of the amino-nitro-imidazole (86) into the chloroacetamido derivative (115) followed by reaction with cyanide ion. In practice, reaction of the amino-nitro-imidazole (86) with sodium hydride followed by chloroacetyl chloride afforded a moderate yield of a brown crystalline solid which gave accurate mass data consistent with the expected molecular formula $C_6H_7ClN_4O_3$, corresponding to the amide structure (115). The spectroscopic properties of the product was also in accord with this structure. Its i.r. spectrum showed carbonyl absorption at 1710 cm^{-1} as well as bands at 1500 and 1350 cm^{-1} due to a nitro-group. The ^1H n.m.r. showed one-, two- and three-proton singlets at $\delta 7.80$, 4.41 and 3.53 due to the imidazole ring CH, the methylene group in the side chain, and the imidazole ring N-methyl substituents respectively. A broad singlet at $\delta 10.80$ was also observed and was attributed to the NH substituent in the side





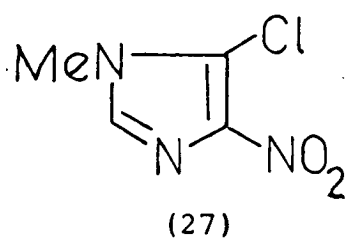
- (i) NaH, PhCCH₂Br .
- (ii) reductive cyclisation .
- (iii) H₂SO₄ .

Scheme 38

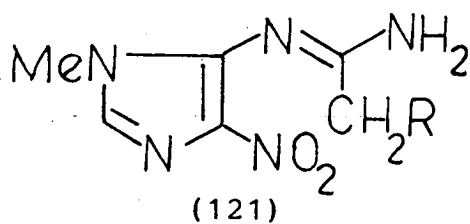
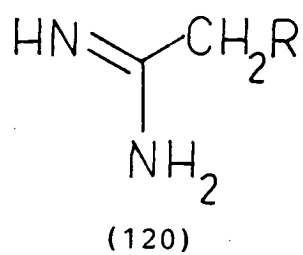
chain. The attempted nucleophilic displacement of the chlorine atom in the chloroacetamido-nitro-imidazole (115) with cyanide ion failed to afford the required cyanoacetamido-nitro-imidazole (114). Thus stirring the chloroacetamido-nitro-imidazole (115) with aqueous ethanolic potassium cyanide at 30° for 45 min gave, after workup, only a high recovery of the unreacted starting-material (115). This failure to obtain the cyanoacetamido-nitro-imidazole (114) prevented the investigation of its cyclisation to the N-oxygenated imidazopyrazines (90b) and/or (116).

In a further attempt to develop a viable synthetic route to N-oxygenated imidazo[4,5-b]pyrazines (Scheme 38) the synthesis of the phenacylamino-nitro-imidazole (117) was investigated with a view to attempting its reductive cyclisation through the hydroxyamino-imidazole intermediate (118) to give the N-hydroxy-imidazo[4,5-b]pyrazine (119) in an analogous fashion to its N-tosyl derivative as already discussed (see page 47 and Scheme 34). However the attempted reaction of the amino-nitro-imidazole (86) with sodium hydride followed by 2-bromoacetophenone failed to afford the expected phenacylamino-nitro-imidazole (117), the starting amine (86) being recovered unchanged in high yield. The hydrolytic conversion of the previously prepared tosyl derivative (106) (see page 47) into the phenacylamino-nitro-imidazole (117) was also unsuccessful. Thus treating the tosylamino-imidazole (106) at 100° with concentrated sulphuric acid in glacial acetic acid gave after workup, only an intractable brown oil whose t.l.c. showed it to be a multicomponent mixture which was not further investigated.

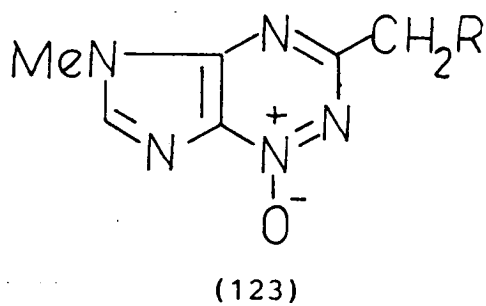
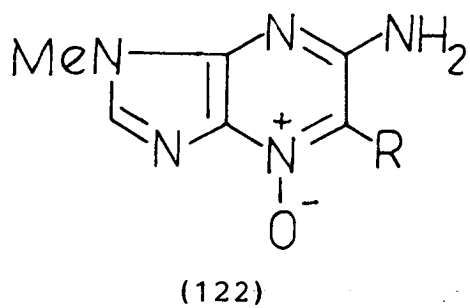
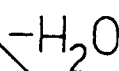
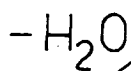
The failure of the foregoing synthetic approaches to N-



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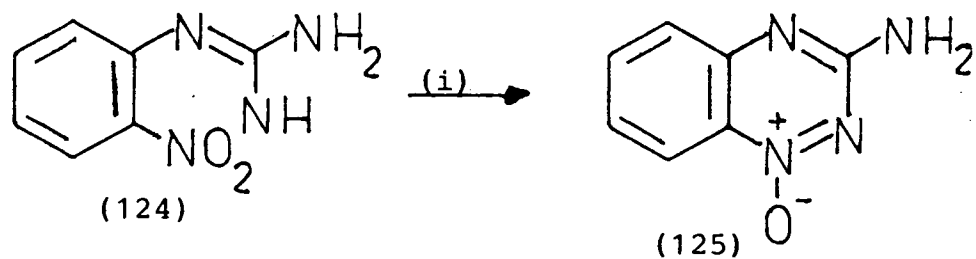


(i)



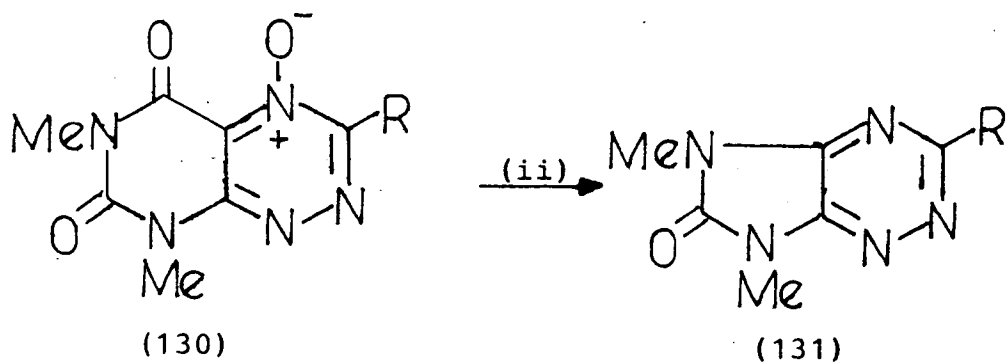
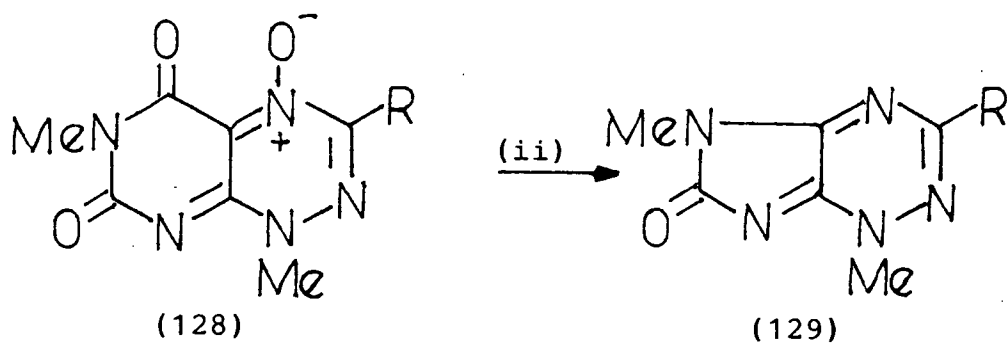
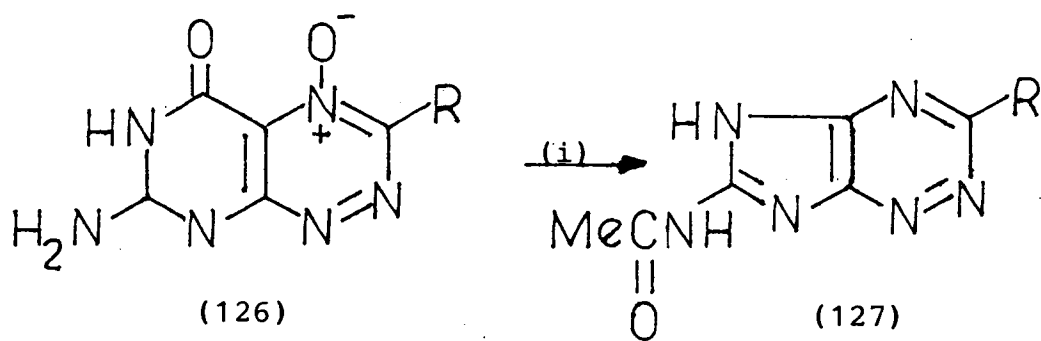
(i) base.

Scheme 39



(i) NaOH, H₂O, heat.

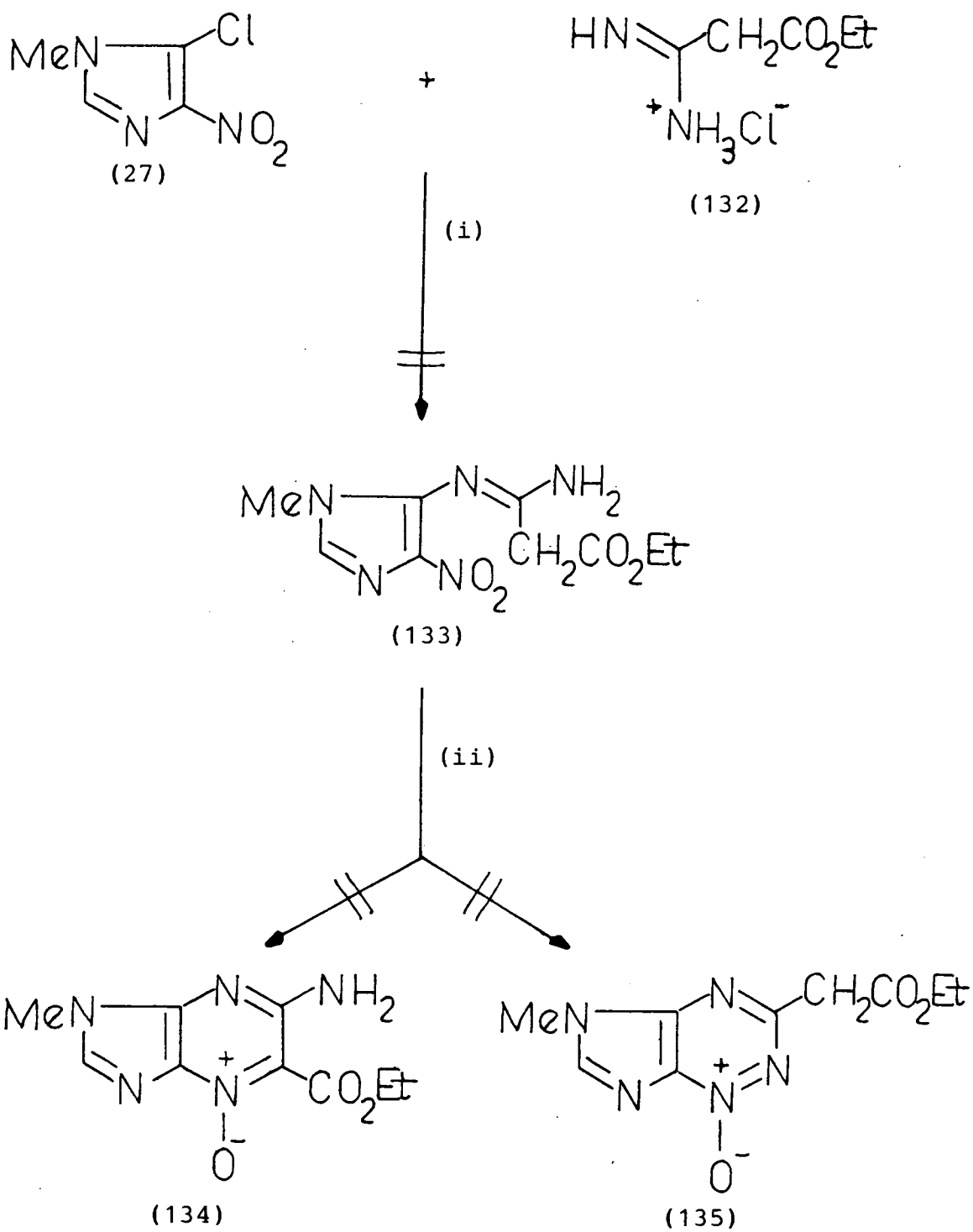
Scheme 40



(i) Ac₂O, heat, 3h.

(ii) NaOH, EtOH, heat.

Scheme 41



(i) Et_3N .

(ii) base.

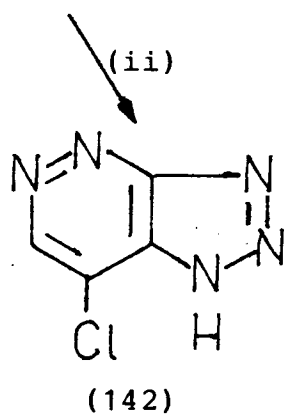
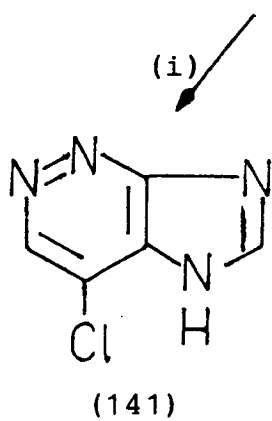
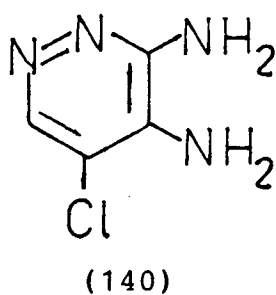
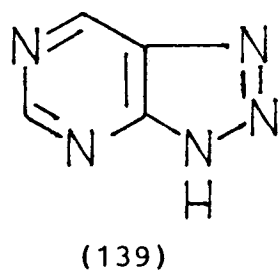
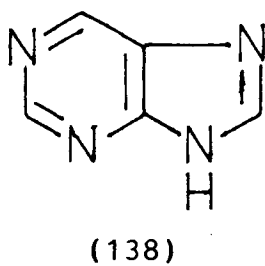
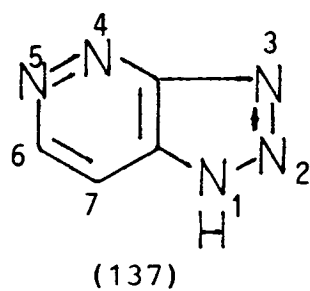
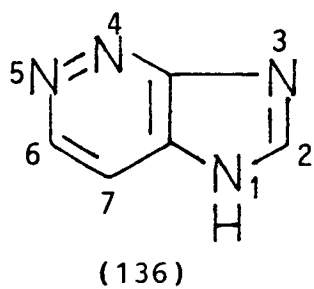
Scheme 42

oxygenated imidazo[4,5-b]pyrazines prompted yet another synthetic strategy (Scheme 39) involving the reaction of the chloro-nitro-imidazole (27) with acetamidine derivatives (120) to give N-4-nitroimidazol-5-yl-acetamidines (121) suitably constituted for base-catalysed cyclisation to imidazo[4,5-b]pyrazine N-oxides (122), or alternatively, imidazo[4,5-e]-1,2,4-triazine N-oxides (123). N-Oxygenated 6-azapurine derivatives of the latter type have not been reported in the literature hitherto. The cyclisation of the nitro-imidazolyl-acetamidines (121) through the amino-group rather than the methylene substituent to give 6-azapurine N-oxides (123) would be analogous to the known⁸³ base-catalysed cyclisation (Scheme 40) of N-2-nitrophenylguanidine (124) to 3-aminobenzo-1,2,4-triazine 1-N-oxide (125). It was later shown⁸⁴ that N-2-nitrophenylguanidine (124) could be prepared from 2-nitroaniline and cyanamide or sodium cyanamide and cyclised in situ to the aminobenzo-triazine N-oxide (125).

Yoneda et al.⁸⁵ have reported the synthesis (Scheme 41) of imidazo[4,5-e]-1,2,4-triazines (127) in moderate yield by the acetic anhydride catalysed ring-contraction of pyrimido[5,4-e]-1,2,4-triazine 4-N-oxides (126). The same workers⁸⁵ also demonstrated the base-catalysed ring-contraction of toxoflavin 4-N-oxides (128) and fervenulin 4-N-oxides (130) to imidazo[4,5-e]-1,2,4-triazine derivatives (129) and (131).

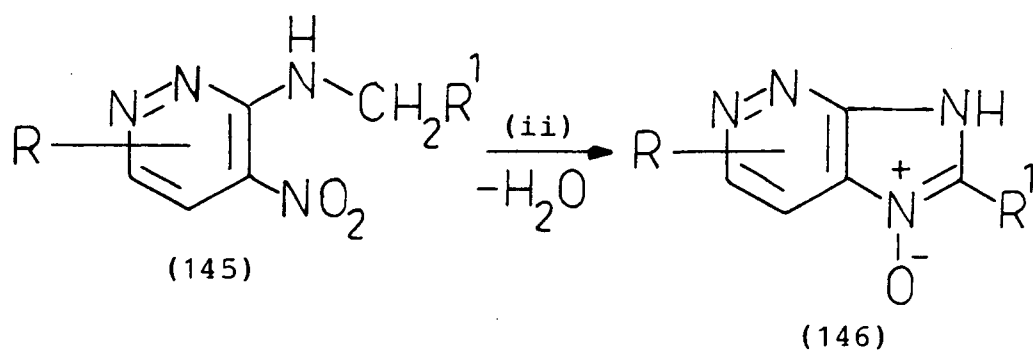
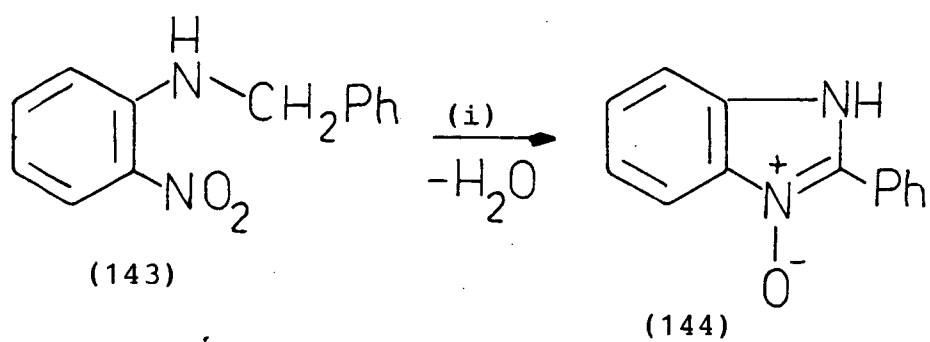
It was decided to evaluate the potential (Scheme 39) of N-4-nitroimidazol-5-yl-acetamidines (121) for the synthesis of imidazo[4,5-b]pyrazine N-oxides (122) and/or imidazo[4,5-e]-1,2,4-triazine N-oxides (123) using (Scheme 42) the ethoxycarbonyl derivative (133). This previously unknown compound was

chosen because its suitably activated methylene centre should promote its base-catalysed cyclisation to the imidazo[4,5-b]pyrazine N-oxide carboxylic ester (134) and because it should be readily synthesised by the base-catalysed condensation of the known⁸⁶ ethoxycarbonylacetamidine hydrochloride (132) with the chloro-nitro-imidazole (27). In practice, the attempted reaction of the latter with the acetamidine hydrochloride (132) in dimethylformamide in the presence of triethylamine at room temperature gave only the unreacted chloro-nitro-imidazole (27) and intractable gums from which no identifiable material could be obtained. The isolation of the unreacted starting-material (27) under room temperature conditions prompted the repetition of the reaction at elevated temperature. However heating the chloro-nitro-imidazole (27) with the acetamidine hydrochloride (132) under reflux in ethanol in the presence of triethylamine afforded only a good recovery of the starting imidazole (27) and no trace of the required nitro-imidazolyl-acetamidine (133). In view of the failure of the chloro-nitro-imidazole (27) to react with the acetamidine hydrochloride (132) under conditions which should have promoted the ready formation of the nitro-imidazolyl-acetamidine (133) it was decided to abandon the general synthetic strategy for imidazo[4,5-b]pyrazine N-oxides (122) and/or imidazo[4,5-e]-1,2,4-triazine N-oxides (123) as outlined in Scheme 39.



(i) $(\text{EtO})_3\text{CH}$, heat, 1h.

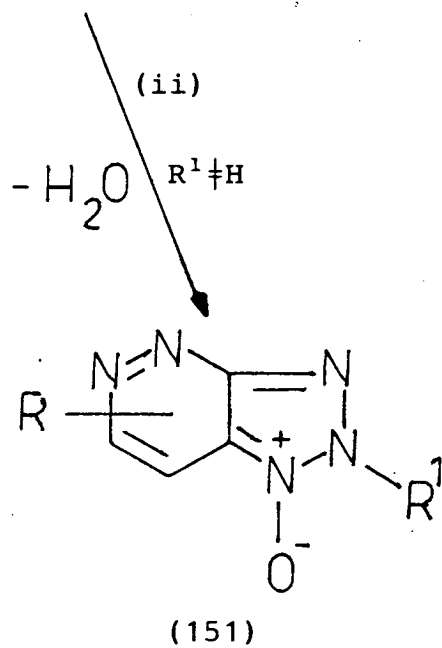
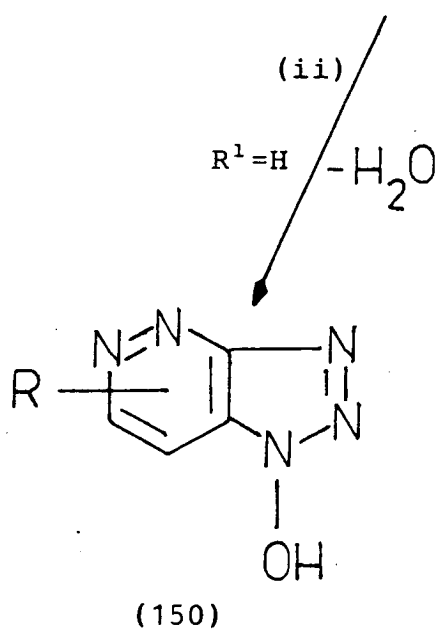
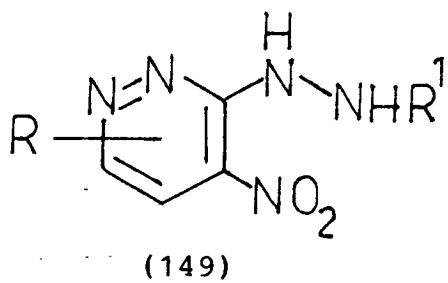
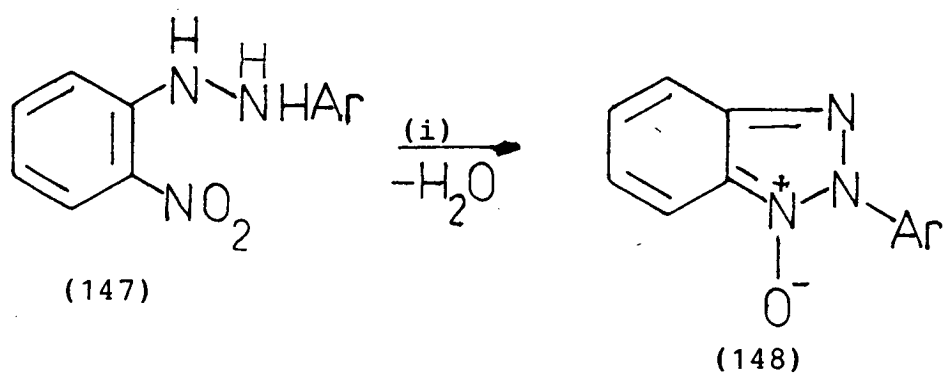
(ii) NaNO_2 , H_2SO_4 .



(i) NaOH, MeOH.

(ii) base.

Scheme 44



(i) AcOH, heat.

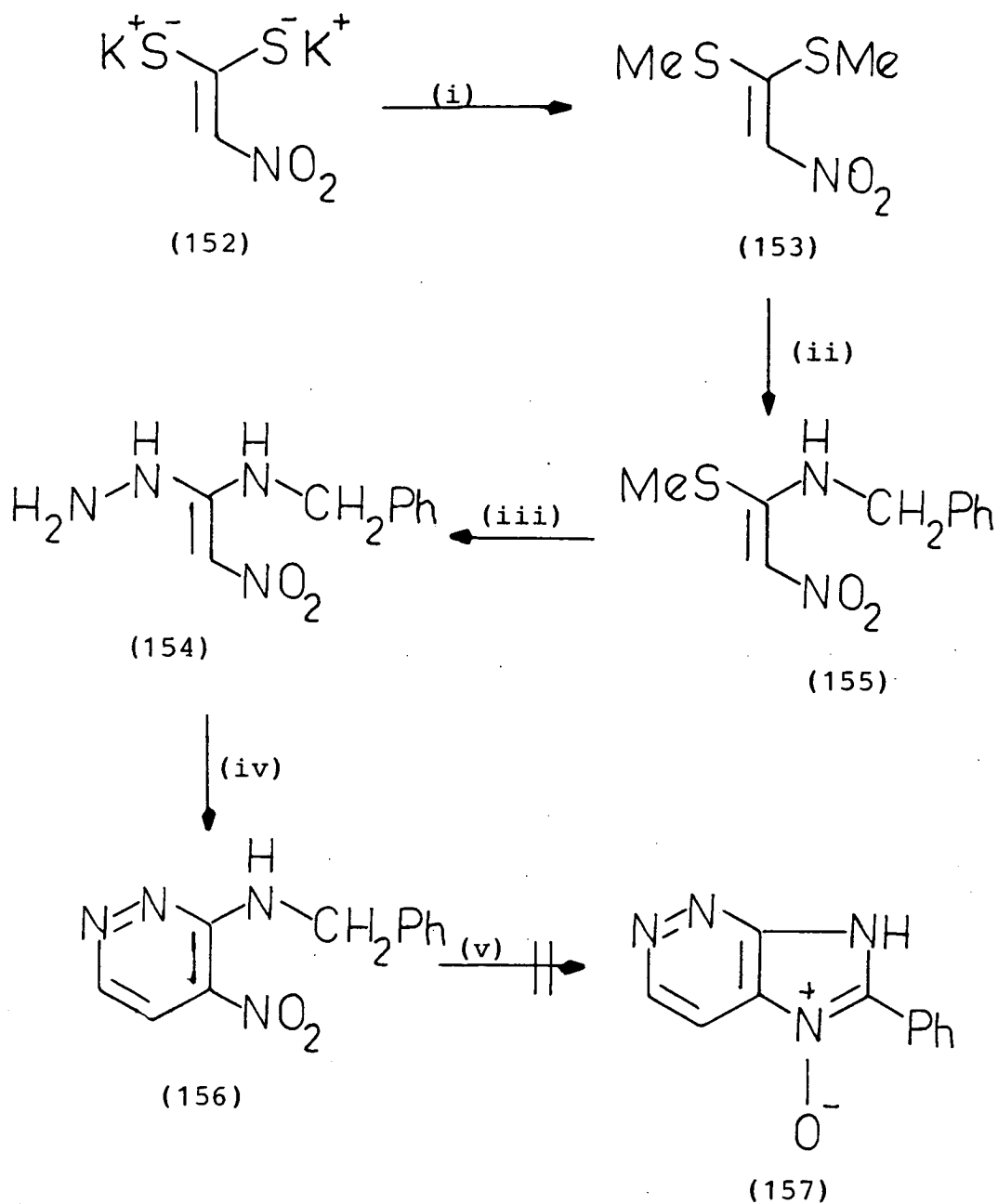
(ii) base.

Scheme 45

(iv) Investigations of New Synthetic Approaches to N-Oxygenated Imidazo[4,5-c]pyridazines and N-Oxygenated 1,2,3-Triazolo[4,5-c]pyridazines

Derivatives (Scheme 43) of the imidazo[4,5-c]pyridazine and 1,2,3-triazolo[4,5-c]pyridazine ring systems (136) and (137) are of interest because of their isosteric relationship to derivatives of the biologically important purine and 8-azapurine ring systems (138) and (139). Castle and his co-workers^{87,88} have reported the synthesis (Scheme 43) in moderate to good yields of imidazo[4,5-c]pyridazines [e.g. (141)] and 1,2,3-triazolo[4,5-c]pyridazines [e.g. (142)] by the ring closure of 3,4-diaminopyridazines [e.g. (140)] with reagents such as ethyl orthoformate and by diazotative cyclisation respectively. In contrast, the synthetically and biologically more interesting N-oxygenated derivatives of imidazo[4,5-c]pyridazines and 1,2,3-triazolo[4,5-c]pyridazines do not appear to have been described in the literature to date and it was therefore of interest to develop a potentially general synthetic strategy for such molecules.

The new general synthetic approaches to N-oxygenated imidazo[4,5-c]pyridazines and 1,2,3-triazolo[4,5-c]pyridazines chosen for study (Schemes 44 and 45) were based on base-catalysed cyclodehydration reactions of suitably functionalised nitro-pyridazine derivatives. Thus, by analogy with the known⁴³ base-catalysed cyclisation of N-alkyl 2-nitroanilines to benzimidazole N-oxides exemplified (Scheme 44) by the methanolic sodium hydroxide catalysed conversion of N-benzyl-2-nitroaniline (143) into 2-phenylbenzimidazole 1-N-oxide (144), it was



(i) Me_2SO_4 , MeOH .

(ii) PhCH_2NH_2 , EtOH , heat, 4h.

(iii) $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, EtOH , heat, 1h.

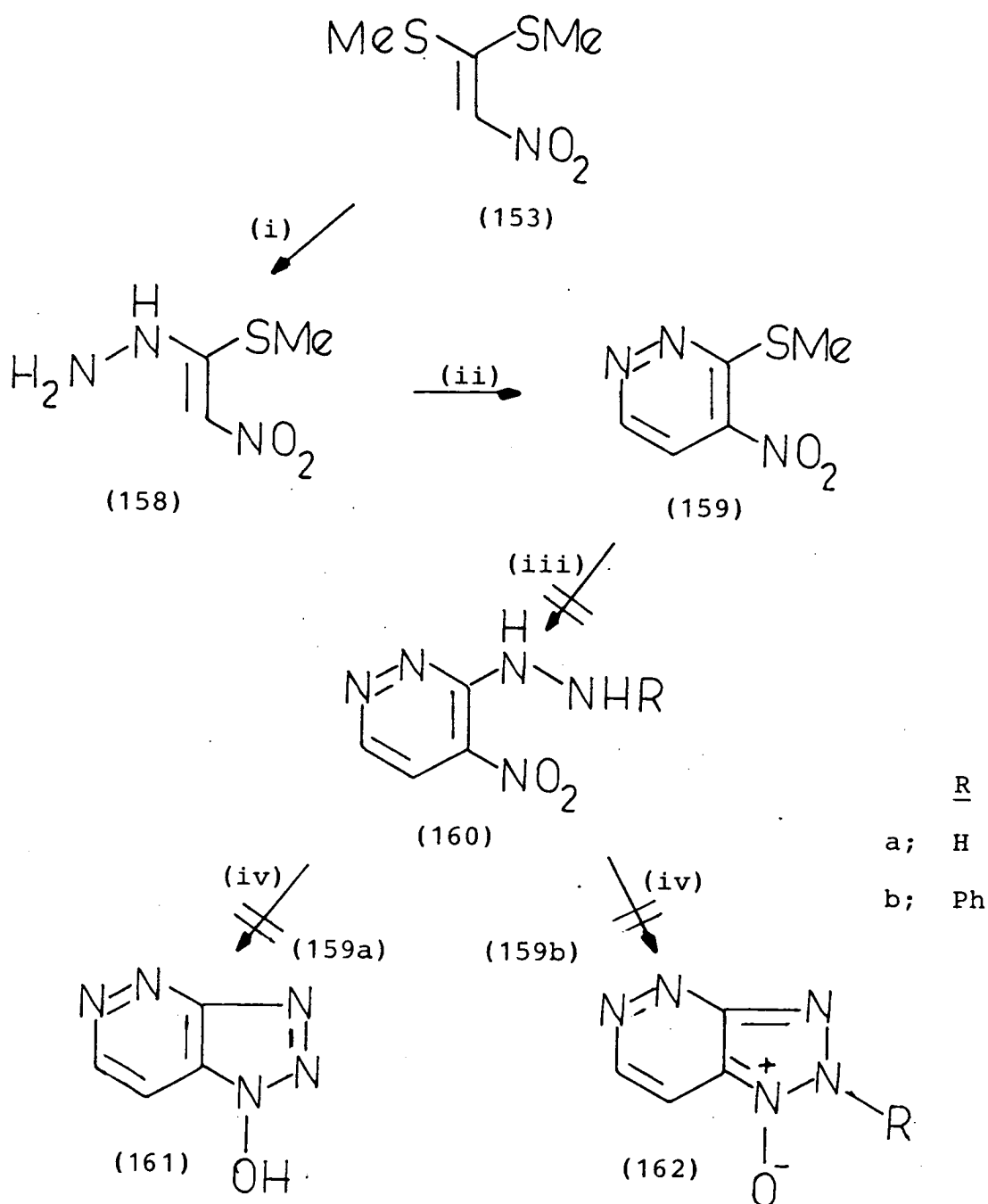
(iv) $\text{O}=\text{CHCH}=\text{O}$, H_2O , C_6H_6 , benzyltrimethylammonium hydroxide.

(v) KOH , MeOH , heat.

Scheme 46

anticipated that 3-alkylamino-4-nitropyridazines (145) would cyclise in the presence of basic catalysts to afford an unambiguous synthesis of imidazo[4,5-c]pyridazine 1-N-oxides (146). Similarly, by analogy with the known²⁹ base-catalysed cyclisation (Scheme 18) of 2-nitrophenylhydrazine (62) to 1-hydroxybenzo-1,2,3-triazole (63) and the cyclisation (Scheme 45) of 2-nitrohydrazinobenzenes (147) to benzo-1,2,3-triazole N-oxides (148),⁹⁰ 3-hydrazino-4-nitropyridazines (149) were expected to undergo cyclodehydration to N-hydroxy-1,2,3-triazolo[4,5-c]pyridazines (150) and 1,2,3-triazolo[4,5-c]pyridazine 1-N-oxides (151).

The resistance⁹¹ of simple pyridazine derivatives to nitration required the synthesis of aminated nitropyridazines of the types (145) and (149) needed for study, by alternative routes (Schemes 46 and 47) based on the work of Hamberger and his co-workers.⁹² These authors showed that the known⁹³ benzylamino-methylthio-nitroethene (155), readily accessible from the nitro-ethene-dithiolate (152)⁹⁴ through the nitro-ketene dimethylthioacetal (153),⁹⁵ reacts with hydrazine monohydrate to afford the benzylamino-hydrazino-nitroethene (154) in good yield. Reaction of the aminohydrazino-nitroethene (154) with glyoxal under conditions of phase-transfer catalysis⁹² afforded a moderate yield of a product formulated as 3-benzylamino-4-nitropyridazine (156). In the present studies repetition of this sequence of reactions described in the literature⁹² afforded a product whose spectroscopic properties were entirely consistent with its formulation⁹² as the benzylamino nitropyridazine (156). In particular its mass spectrum showed the expected molecular ion at m/e 230, and its ¹H n.m.r. spectrum



(i) $\text{NH}_2\text{NH}_2, \text{H}_2\text{O}, \text{EtOH}, \text{heat}, 0.5\text{h}.$

(ii) $\text{O}=\text{CHCH}=\text{O}, \text{H}_2\text{O}, \text{C}_6\text{H}_6, \text{benzyltrimethylammonium hydroxide and}$
 $\text{O}=\text{CHCH}=\text{O}, \text{H}_2\text{O}, \text{EtOH}, \text{Na}_2\text{CO}_3, 8^\circ, 45 \text{ min}.$

(iii) $\text{RNHNH}_2, \text{EtOH}, \text{heat}.$

(iv) base.

Scheme 47

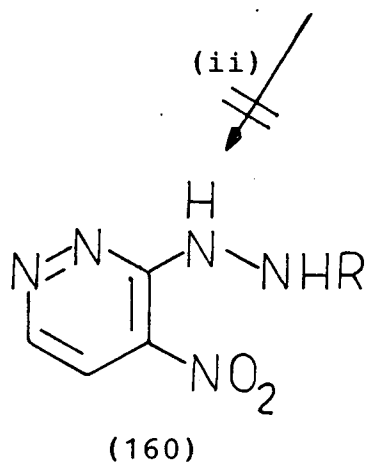
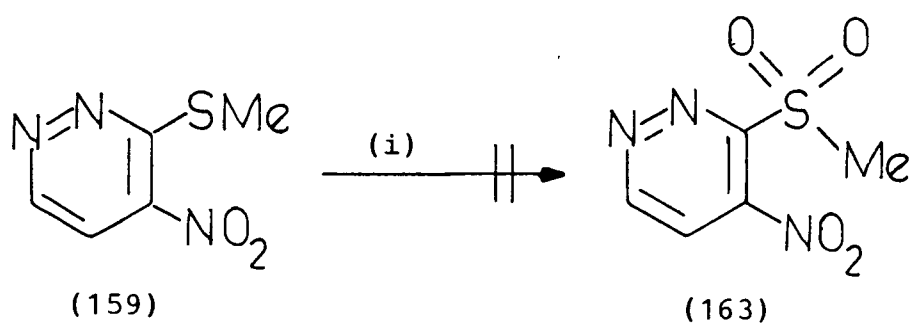
in addition to a five-proton multiplet due to the phenyl protons of the benzylamine substituent, showed two one-proton doublets at δ 8.80 and 8.07 assignable to H-5 and H-6 of the pyridazine (156). A broad one-proton singlet at δ 8.70 attributable to the NH-substituent of the pyridazine (156) was also observed.

Unfortunately the benzylamino-nitropyridazine (156), though suitably constituted for base-catalysed cyclisation to the imidazo[4,5-c]pyridazine N-oxide (157), failed to afford this product when treated with methanolic potassium hydroxide under conditions known⁴³ to effect the analogous transformation [Scheme 44; (143)→(144)]. The only materials isolated in the case of the benzylamino-nitropyridazine (156) were intractable solids whose t.l.c. showed them to be multicomponent mixtures from which no identifiable material could be obtained.

Hamberger and his co-workers⁹² also reported (Scheme 47) that reaction of the nitroketene dimethylthioacetal (153) with hydrazine monohydrate affords an oily product formulated as the hydrazino-methylthio-nitroethene (158). This interesting product was further shown⁹² to react with glyoxal in the presence of sodium carbonate to yield a compound assigned the methylthio-nitropyridazine structure (159). It was decided to repeat the published procedure⁹² for the synthesis of the methylthio-nitropyridazine (159) in the expectation that it would undergo nucleophilic displacement at the activated methylthio substituent to afford 3-hydrazino-4-nitropyridazines (160) suitable for base-catalysed cyclisation to N-oxygenated imidazo[4,5-c]pyridazines (161) and (162).

Reaction of the nitroketene dimethylthioacetal (153) with hydrazine monohydrate as described in the literature⁹² gave the oily hydrazino-methylthio-nitroethene (158) which tended to decompose on storage and was reacted without purification with glyoxal in the presence of sodium carbonate to afford a low yield of a product which had a melting-point somewhat lower than that reported in the literature⁹² for the methylthio-nitropyridazine (159). However its mass spectrum showed the expected molecular ion at m/e 171 and its ^1H n.m.r. spectrum exhibited two one-proton doublets at δ 9.47 and 8.37 due to H-5 and H-6 of the pyridazine ring as well as a three-proton singlet assignable to the protons of the methylthio-substituent. The fully coupled and decoupled ^{13}C n.m.r. spectra of the compound also showed carbon resonances fully in accord with its formulation as 3-methylthio-4-nitropyridazine (159). The yield of this product was found in the present studies to be much improved compared to that of the literature method⁹² by carrying out the reaction of the hydrazino-methylthio-nitroethene (158) with glyoxal in the presence of benzyltrimethylammonium hydroxide under phase-transfer catalytic conditions.

The attempted nucleophilic displacement of the methylthio substituent in the nitropyridazine (159) by hydrazine monohydrate to give the desired hydrazino-nitropyridazine (160a) was unsuccessful. Thus, heating the methylthiopyridazine (159) with hydrazine monohydrate in ethanol afforded an unresolvable multicomponent mixture from which no identifiable material could be obtained. Similarly carrying out this reaction under milder conditions by stirring the pyridazine

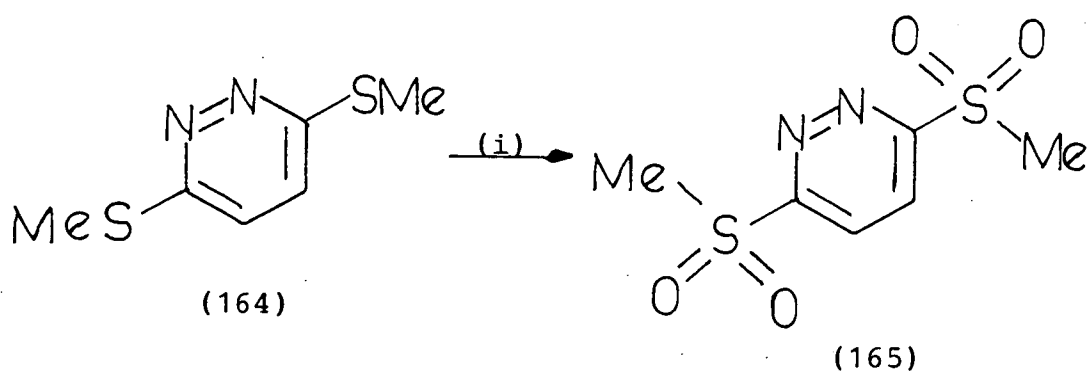


R
 a; H
 b; Ph

(i) AcOH, H₂O₂, 50°, 19h.

(ii) RNHNH₂, EtOH, heat.

Scheme 48



(i) H₂O₂, AcOH.

Scheme 49

(159) with hydrazine monohydrate in ethanol at room temperature also afforded an unresolvable multicomponent mixture. The failure of these attempts to convert the methylthio-nitropyridazine (159) into the hydrazino-nitropyridazine (160a) prevented the study of the base-catalysed cyclisation of the latter to the N-hydroxyimidazo[4,5-c]pyridazine (161).

The attempted reaction of the methylthio-nitropyridazine (159) with phenylhydrazine under conditions expected to result in the nucleophilic displacement of the methylthio-substituent to give the required hydrazino-nitropyridazine (160b) was also unsuccessful. Thus, heating the methylthio-nitropyridazine (159) under reflux with phenylhydrazine in benzene gave only intractable gums and oils which yielded no material identifiable as the required hydrazino-nitropyridazine (160b). The consequent unavailability of this compound therefore prevented the study of its cyclisation to the 1,2,3-triazolo[4,5-c]pyridazine N-oxide (162).

The failure of the hydrazino-nitropyridazine (159) to undergo nucleophilic displacement reactions with hydrazines (Scheme 47) could be attributed to the methylthio substituent being deactivated to nucleophilic displacement by the pyridazine ring system. In an attempt to activate this methylthio substituent its conversion (Scheme 48) to the sulphone (163) was considered. The sulphone (163) should be more reactive towards nucleophilic displacement reactions giving the desired hydrazino-nitropyridazines (160), the base-catalysed cyclisation of which could provide synthetic routes to the N-hydroxyimidazo[4,5-c]pyridazine and the 1,2,3-triazolo[4,5-c]pyridazine N-

oxide (161) and (162) as outlined in Scheme 47.

In practice, the attempted oxidation of the methylthio-nitropyridazine (159) to the sulphone [Scheme 48; (163)], using conditions employed by Kumagia⁹⁶ (Scheme 49) for the oxidation of the dimethylthiopyridazine (164), failed to give the desired product and thus prevented the proposed investigations into nucleophilic displacement reactions of the sulphone substituent in the pyridazine (163) with hydrazines. The only product isolated from the attempted oxidation of the methylthio-nitropyridazine (159) with hydrogen peroxide in glacial acetic acid was a yellow oil from which no identifiable material could be obtained.

Abushanab and Bindra⁹⁷ have also reported difficulties in the nucleophilic displacement of methylthio substituents from heterocyclic systems and these workers also found that the sulphone and sulphonyl derivatives were also unreactive towards nucleophilic displacement in such systems.

(v) ExperimentalN,N-Dimethyloxamide (25)

N,N-Dimethyloxamide (25) was prepared (yield 90%) by the reaction of diethyl oxalate with aqueous methylamine as described by Wallach,^{59,60} and had m.p. 215-217° (lit.,^{59,60} 209-210°).

5-Chloro-1-N-methylimidazole (26)

5-Chloro-1-N-methylimidazole (26) was prepared (yield 41%) by the reaction of N,N-dimethyloxamide (25) with phosphorus pentachloride as described by Wallach,^{59,60} and was obtained as an oil, b.p. 74°/1.5 mmHg (lit.,^{59,60} 205°/760 mmHg).

5-Chloro-1-N-methyl-4-nitroimidazole (27)

5-Chloro-1-N-methyl-4-nitroimidazole (27) was prepared (yield 96%) by the nitration of 5-chloro-1-N-methylimidazole (26) as described by Sarasin and Wegmann,⁶¹ and had m.p. 138-142° (lit.,⁶¹ 147-148°).

5-Cyano-1-N-methyl-4-nitroimidazole (28)

5-Cyano-1-N-methyl-4-nitroimidazole (28) was prepared (yield 90%) by the reaction of 5-chloro-1-N-methyl-4-nitroimidazole (27) with potassium cyanide as described by Sarasin and Wegmann,⁶¹ and had m.p. 135-138° (lit.,⁶¹ 141-142°).

1-N-Methyl-4-nitroimidazole-5-carboxylic acid (29)

1-N-Methyl-4-nitroimidazole-5-carboxylic acid (29) was prepared (yield 87%) from 5-cyano-1-N-methyl-4-nitroimidazole

(28) as described by Mann and Porter,⁵⁸ and had m.p. 159-160° (lit.,⁵⁸ 161°).

1-N-Methyl-4-nitroimidazole-5-carbonyl chloride (19)

1-N-Methyl-4-nitroimidazole-5-carbonyl chloride (19) was prepared (yield 95%) by the reaction of 1-N-methyl-4-nitroimidazole-5-carboxylic acid (29) with thionyl chloride as described by Mann and Porter,⁵⁸ and had m.p. 58-60° (lit.,⁵⁸ 62-62.5°).

1-N-Methyl-4-nitroimidazole-5-(N-cyanomethyl,N-methyl)carboxamide (31)

Methylaminoacetonitrile hydrochloride (3.2 g, 0.03 mol) was added to a stirred slurry of fused sodium acetate (11.1 g, 0.135 mol) in glacial acetic acid (60.0 ml) and the mixture treated in portions with 1-N-methyl-4-nitroimidazole-5-carbonyl chloride (19) (5.7 g, 0.03 mol). This mixture was stirred for a further 3h after the addition was complete, then the resulting suspension evaporated and the residue treated with water (25.0 ml) to give a solid. This was combined with a second crop isolated by toluene trituration of the gummy solid, obtained on extraction of the filtrate with methylene chloride (3x50.0 ml), to give the imidazole-(N-cyanomethyl,N-methyl)carboxamide (31) (5.6 g; 84%) which formed colourless crystals m.p. 195-196° (from ethanol-dimethylformamide),

ν_{\max} 1660 (CO) and 1515 and 1325 (NO_2) cm^{-1} ; δ_{H} [$(\text{CD}_3)_2\text{SO}$] 7.95 (1H, s, imidazole CH), 4.70 (2H, s, CH_2), 4.58 (2H, s, CH_2), 3.64 (3H, s, imidazole NCH_3), 3.32 (3H, s, NCH_3), and 2.96 (3H, s, NCH_3), changing at 90° to δ_{H} [$(\text{CD}_3)_2\text{SO}$] 7.98 (1H, s, imiadazole CH), 4.62 (2H, s, CH_2), 3.66 (3H, s, imidazole NCH_3), and 3.04 (3H, s, NCH_3), δ_{C} [$(\text{CD}_3)_2\text{SO}$] 159.77 (C=O), 143.10 (C-4), 138.47 (C-2), 125.40 (C-5), 115.76 ($\text{C}\equiv\text{N}$), 35.7 (CH_2), 35.16 (NCH_3) and 33.02 (NCH_3).

Found: C, 43.3; H, 4.1; N, 31.8%; M^+ , 223.

$\text{C}_8\text{H}_9\text{N}_5\text{O}_3$ requires: C, 43.1; H, 4.1; N, 31.4%; M, 223.

The Attempted Base-catalysed Cyclisation Reactions of 1-N-Methyl-4-nitroimidazole-5-(N-cyanomethyl,N-methyl)carboxamide
(31)

(i) Using sodium ethoxide as the base

(a) A suspension of the imidazole-carboxamide (31) (2.7 g, 0.012 mol) in absolute ethanol (25.0 ml) was heated under reflux and treated with a solution of sodium (1.5 g, 0.064 g.atom) in absolute ethanol (35.0 ml) and the resulting solution heated under reflux for 1h. The mixture was evaporated, the residue treated with water (20.0 ml) and the resulting solid collected to give 1-N-methyl-4-(1-N-methyl-5-N-methylcarbamoylimidazol-4-yl)azoimidazole-5-N-methylcarboxamide (34) (0.91 g; 50%)

which formed yellow crystals m.p. 263-264° (from ethanol-dimethylformamide), ν_{\max} 3290 (NH) and 1660 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.30 (2H, s, imidazole CH), 7.94 (2H, br, J2Hz, NHCH_3), 3.94 (6H, s, imidazole NCH_3), 3.60 (3H, s, NCH_3), 3.50 (3H, s, NCH_3), 3.00 (3H, s, NCH_3), and 2.91 (3H, s, NCH_3), changing at 85° to $\delta[(\text{CD}_3)_2\text{SO}]$ 8.28 (2H, s, imidazole CH) 7.93 (2H, t, J2Hz, NHCH_3), 3.95 (6H, s, imidazole NCH_3), 3.49 (3H, d, J2Hz, NCH_3) and 2.94 (3H, d, J2Hz, NCH_3).

Found: C, 46.7; H, 5.3; N, 36.3%; M^+ , 304.1391.
 $\text{C}_{12}\text{H}_{16}\text{N}_6\text{O}_2$ requires: C, 47.4; H, 5.3; H, 36.8%; M, 304.1396.

The aqueous phase was extracted with ethyl acetate (3x50.0 ml) to give a gummy solid (0.2 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multi-component mixture which was not further investigated.

The aqueous mother liquor was acidified with concentrated hydrochloric acid and the solution extracted with ethyl acetate (3x50.0 ml) to give a gummy solid (0.1 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multi-component mixture which was not further investigated.

(b) A stirred suspension of the imidazole-carboxamide (31) (0.45 g, 0.002 mol) in absolute ethanol (5.0 ml) was treated dropwise at room temperature with a solution of sodium (0.18 g, 0.008 g.atom) in absolute ethanol (5.0 ml) and the mixture stirred, with protection from atmospheric moisture, for 5h and left at room temperature for 16h. The mixture was evaporated and the residue was treated with water (5.0 ml) and the solution neutralised by treatment with concentrated hydrochloric acid, followed by solid sodium acetate. The neutral solution was

then extracted with methylene chloride (3x25.0 ml) to give a brown oil (0.08 g) whose t.l.c. in ethanol over silica showed it to be an unresolvable multicomponent mixture which yielded no identifiable material.

The aqueous mother liquor was evaporated and the residue extracted with boiling ethyl acetate to give a brown oil (0.2 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture, which was not further investigated.

(ii) Using sodium carbonate as the base

A suspension of the imidazole-carboxamide (31) (0.90 g, 0.004 mol) in ethanol (100 ml) was heated under reflux, treated with aqueous 0.5M sodium carbonate solution (16.0 ml), and the resulting green solution heated under reflux for 3h. The final brown solution was evaporated and the residue treated with water (10.0 ml) to give a yellow solid which was combined with a second crop obtained by extracting the aqueous mother liquor with methylene chloride (3x25.0 ml) and triturating the residue obtained with ethyl acetate, to give an uncharacterised solid (0.10 g; 18%) which formed yellow crystals m.p. 268-270° (from ethanol-dimethylformamide), ν_{\max} 1650 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 7.94 (1H, br, J1Hz, NHCH_3), 3.94 (3H, s, NCH_3) and 2.88 (3H, d, J4Hz, NHCH_3).

Found: C, 46.0; H, 4.2; N, 38.9%; M^+ , 288.

$\text{C}_{11}\text{H}_{12}\text{N}_8\text{O}_2$ requires: C, 45.8; H, 4.2; N, 38.9%; M, 288.

Evaporation of the ethyl acetate mother liquor gave an intractable brown gum (0.11 g) which was not further investigated.

The aqueous mother liquor was acidified with concentrated hydrochloric acid and extracted with methylene chloride (3x25.0 ml) to give an intractable red gum (0.03 g) which was not further investigated.

(iii) Using sodium hydride as the base

A suspension of sodium hydride (0.12 g, 0.0048 mol) in dry dimethylformamide (2.0 ml) was stirred and treated at room temperature with a suspension of the imidazole-carboxamide (31) (0.89 g, 0.004 mol) in dry dimethylformamide (5.0 ml). This mixture was stirred with protection from atmospheric moisture for 18h. The resulting dark suspension was treated with water (10.0 ml) to give an uncharacterised green solid (0.044 g; 4%) which formed green crystals m.p. 283-284° (decomp.) (from ethanol-dimethylformamide), ν_{\max} 3360 (NH), 2210 (CN) and 1660 (CO) cm^{-1} .

Found: C, 45.2; H, 4.2; N, 38.5%; M^+ , 288.

$C_{11}H_{12}N_8O_2$ requires: C, 45.8; H, 4.2; N, 38.9%; M, 288.

Extraction of the aqueous mother liquor with methylene chloride before and after acidification with concentrated hydrochloric acid gave only low yields of intractable oils.

(iv) Using piperidine as the base

A suspension of the imidazole-carboxamide (31) (0.45 g, 0.002 mol) in ethanol (50.0 ml) was heated under reflux, treated with piperidine (0.69 g, 0.008 mol) and the mixture heated under reflux for 2h. The mixture was then evaporated and the brown oil obtained triturated with toluene to give a solid which was combined with a second crop obtained by

evaporating the toluene filtrate and treating the resulting residue with aqueous 2M hydrochloric acid, to give unreacted starting-material (0.19 g; 42%), m.p. 178-183°, identical (m.p. and i.r. spectrum) to an authentic sample.

The acidic aqueous mother liquor was extracted with methylene chloride (3x25.0 ml) to give a brown oil (0.15 g) whose t.l.c. in ether over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

(v) Using diazabicyclo[3,4,0]non-5-ene (DBN) as the base

(a) A stirred solution of the imidazole-carboxamide (31) (0.45 g, 0.002 mol) in dry dimethylformamide (5.0 ml) was treated dropwise, with protection from atmospheric moisture at 0-10° (ice bath), with DBN (0.29 g, 0.0022 mol) and the mixture stirred at 0-10° for 1h. The resulting suspension was treated with water (10.0 ml) and filtered to remove unreacted starting-material more of which was obtained by extracting the aqueous mother liquor with methylene chloride and triturating the brown oil obtained with methylene chloride-ether (total 0.26 g; 57%) m.p. 188-192°, identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the methylene chloride-ether mother liquor gave a low yield of an intractable brown gum, which was not further investigated.

The aqueous mother liquor was acidified using concentrated hydrochloric acid and extracted with methylene chloride to give a low yield of an intractable yellow oil, which was not further investigated.

(b) A solution of the imidazole-carboxamide (31) (0.45 g; 0.002 mol) in dry 1,2-dimethoxyethane (30.0 ml) was heated under reflux and treated with DBN (0.29 g; 0.0022 mol) and the mixture heated under reflux for 6h. The resulting dark solution was evaporated and the residue treated with aqueous 2M hydrochloric acid (5.0 ml) and extracted with ethyl acetate (3x50.0 ml) to yield a brown gummy solid which was triturated with ethanol-light petroleum to give the unreacted starting-material (31) (0.076 g; 17%) m.p. (crystallised sample) 186-188°, identical (m.p. and i.r. spectrum) to an authentic sample.

The ethanolic filtrate was evaporated to give a brown oil whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture, which was not further investigated.

The Attempted Hydrolysis of the Azo-imidazole Derivative (34)

A solution of the azo-imidazole derivative (34) (0.30 g, 0.001 mol) in aqueous 2M sodium hydroxide (10.0 ml) was heated under reflux for 1h. The resulting suspension was filtered to give unreacted starting-material (34) (0.16 g; 53%), m.p. 267-268°, identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous mother liquor was acidified with concentrated hydrochloric acid, filtered to remove solid residue and extracted with methylene chloride (3x25.0 ml) to give a low yield of an intractable oil which was not further investigated.

1-N-Methyl-4-nitroimidazole-5-N-methylcarboxamide (41)

1-N-Methyl-4-nitroimidazole-5-carbonyl chloride (19) (1.5 g, 0.008 mol) was added in portions with stirring at 0° (ice-salt bath) to 25-30% aqueous methylamine solution (5.0 ml) and the resulting suspension stirred at 0° for 5 min. The mixture was filtered and the solid washed with saturated aqueous sodium hydrogen carbonate solution and water, and dried to give 1-N-methyl-4-nitroimidazole-5-N-methylcarboxamide (41) (1.2 g; 83%) which formed cream needles m.p. 204-205° (from ethyl acetate), ν_{\max} 3290 (NH), 1655 (CO) and 1500 and 1345 (NO₂) cm⁻¹, $\delta[(\text{CD}_3)_2\text{SO}]$ 8.84 (1H, br s, NH), 7.82 (1H, s, imidazole CH), 3.64 (3H, s, imidazole NCH₃) and 2.80 (3H, d, J2Hz, NHCH₃).

Found: C, 39.2; H, 4.3; N, 30.3%; M⁺, 184.

C₆H₈N₄O₃ requires: C, 39.1; H, 4.4; N, 30.4%; M, 184.

The Reaction of 1-N-Methyl-4-nitroimidazole-5-N-methylcarboxamide (41) with Ethanolic Sodium Ethoxide

A solution of 1-N-methyl-4-nitroimidazole-5-N-methylcarboxamide (41) (0.92 g, 0.005 mol) in ethanol (12.5 ml) was heated under reflux and treated with a solution of sodium (0.46 g, 0.02 g.atom) in ethanol (12.5 ml). This mixture was heated under reflux for 1h, then evaporated and the residue treated with water (5.0 ml) to give a solid, which was washed with aqueous 2M hydrochloric acid to afford 1-N-methyl-4-(1-N-methyl-5-N-methylcarbamoylimidazol-4-yl)azoimidazole-5-N-methylcarboxamide (34) (0.05 g; 16%) m.p. 264-265° (decomp.)

identical (m.p. and i.r. spectrum) to an authentic sample obtained before.

The basic aqueous mother liquor was extracted with ethyl acetate (3x50.0 ml) to give a brown gum (0.11 g) whose t.l.c. in ethanol over silica showed it to be an unresolvable multi-component mixture, which was not further investigated.

N-Phenacylaniline (45)

N-Phenacylaniline (45) was prepared (yield 98%) by the reaction of phenacyl bromide with aniline as described by Bischler⁶⁴ and had m.p. 89-91° (lit.,⁶⁴ 93°).

The Reaction of 1-N-Methyl-4-nitroimidazole-5-carbonyl chloride (19) with N-Phenacylaniline (45)

A slurry of fused sodium acetate (1.86 g, 0.023 mol) in glacial acetic acid (10.0 ml) was stirred and treated with N-phenacylaniline (45) (1.06 g, 0.005 mol). 1-N-Methyl-4-nitroimidazole-5-carbonyl chloride (19) (0.95 g, 0.005 mol) was added in portions and the mixture was stirred at room temperature for 3h after the addition of the acid chloride (19) was complete. The resulting suspension was evaporated and the residue treated with water (5.0 ml) and extracted with methylene chloride (3x50.0 ml) to give a brown oil (2.2 g). This was triturated with ether-ethyl acetate to give 1-N-methyl-4-nitroimidazole-5-N-phenylcarboxamide (48) (0.16 g; 13%) which formed yellow crystals m.p. 192-193° (from ethanol), ν_{\max} 3295 br (NH), 1680 (CO) and 1510 and 1340 (NO₂) cm⁻¹,

$\delta[(\text{CD}_3)_2\text{SO}]$ 10.91 (1H, s, NH), 8.91 (1H, s, imidazole CH), 7.72-7.14 (5H, m, ArH) and 3.77 (3H, s, NCH_3).

Found: C, 53.5; H, 4.1; N, 22.8%; M^+ , 246.

$\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}_3$ requires: C, 53.7; H, 4.1; N, 22.8%; M, 246.

The ether-ethyl acetate mother liquor was evaporated to give a red glassy solid (1.4 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture, which was not further investigated.

1-N-Methyl-4-nitroimidazole-5-(N- α -cyanobenzyl, N-methyl-carboxamide) (50)

A slurry of fused sodium acetate (4.1 g, 0.05 mol) in glacial acetic acid (30.0 ml) was stirred and treated in one portion with α -methylaminophenylacetonitrile (49) (3.7 g, 0.025 mol) followed by 1-N-methyl-4-nitroimidazole-5-carbonyl chloride (19) (4.7 g, 0.025 mol) and the mixture stirred at room temperature for 3h. The resulting suspension was evaporated and the residue treated with water (15.0 ml) to give 1-N-methyl-4-nitroimidazole-5-(N- α -cyanobenzyl, N-methyl-carboxamide) (50) (6.6 g; 89%) which formed colourless crystals m.p. 188-189° (from ethanol), ν_{max} 1665 (CO) and 1525 and 1345 (NO_2) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.0 (1H, s, imidazole CH), 7.72 (5H, s, ArH), 7.18 (1H, s, CH), 3.70 (3H, s, imidazole NCH_3) and 2.82 (3H, s, NCH_3).

Found: C, 56.3; H, 4.3; N, 23.4%; M^+ , 299.

$\text{C}_{14}\text{H}_{13}\text{N}_5\text{O}_3$ requires: C, 56.2; H, 4.4; N, 23.4%; M, 299.

The Attempted Base-catalysed Cyclisation of 1-N-Methyl-4-nitroimidazole-5-(N- α -cyanobenzyl,N-methylcarboxamide) (50)

(i) Using sodium carbonate as the base

A suspension of 1-N-methyl-4-nitroimidazole-5-(N- α -cyanobenzyl,N-methylcarboxamide) (50) (0.6 g, 0.002 mol) in ethanol (40.0 ml) was treated with aqueous 0.5M sodium carbonate (8.0 ml) and the mixture heated under reflux for 3h. The mixture was evaporated and the residue treated with water (5.0 ml) and filtered to afford unreacted starting-material (50) (0.03 g; 5%) m.p. 194-196°, identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous mother liquor was extracted with methylene chloride (3x25.0 ml) to give 1-N-methyl-4-nitroimidazole-5-N-methylcarboxamide (41) (0.21 g; 58%) m.p. 115-120°, identical (m.p. and i.r. spectrum) to an authentic sample. Acidification of the aqueous mother liquor with concentrated hydrochloric acid afforded a light brown solid which was combined with a second crop obtained by extracting the acidic aqueous mother liquor with methylene chloride to give benzoic acid (0.13 g; 53%) m.p. 97-99°, identical (m.p. and i.r. spectrum) to an authentic sample.

(ii) Using sodium acetate as the base

A suspension of 1-N-methyl-4-nitroimidazole-5-(N- α -cyanobenzyl,N-methylcarboxamide) (50) (0.5 g, 0.002 mol) in ethanol (40.0 ml) was treated with aqueous 0.5M sodium acetate (8.0 ml) and the mixture heated under reflux for 3h. The

resulting solution was evaporated and the residue treated with water (5.0 ml) and extracted with methylene chloride (3x25.0 ml) to give a gummy brown solid which was crystallised from ethanol to afford 1-N-methyl-4-nitroimidazole-5-N-methylcarboxamide (41) (0.11 g; 30%) m.p. 193-195°, identical (m.p. and i.r. spectrum) to an authentic sample.

The ethanolic filtrate was evaporated to give a brown gum whose t.l.c. in ethanol over silica showed it to be an unresolvable multicomponent mixture, which was not further investigated.

The aqueous mother liquor was acidified with concentrated hydrochloric acid and extracted with methylene chloride (3x25.0 ml) to give benzoic acid (0.05 g; 20%) m.p. (crystallised sample) 110-115°, identical (m.p. and i.r. spectrum) to an authentic sample.

(iii) Using diazabicyclo[3,4,0]non-5-ene (DBN) as the base

A solution of 1-N-methyl-4-nitroimidazole-5-(N- α -cyano-benzyl,N-methylcarboxamide) (50) (0.60 g, 0.002 mol) in dry dimethylformamide (5.0 ml) was treated dropwise with stirring at 0-10° (ice-bath) with DBN (0.28 g, 0.0022 mol) and the mixture stirred for 1.5h at 0-10° (ice-bath) with protection from atmospheric moisture. The resulting yellow-brown solution was treated with water (15.0 ml) and the precipitated solid collected to give unreacted starting-material (50) (0.01 g; 2%) m.p. 178-182°, identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous mother liquor was evaporated and the residue triturated with ethanol-light petroleum to give a solid which

crystallised from ethanol to afford 1-N-methyl-4-nitroimidazole-5-N-methylcarboxamide (41) (0.12 g; 33%), m.p. 194-198°, identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the ethanolic mother liquors gave dark gums whose t.l.c. in ethanol over silica showed them to be multicomponent mixtures containing 1-N-methyl-4-nitroimidazole-5-N-methylcarboxamide (41). These gums were not further investigated.

1,2-Di-(1-N-methyl-4-nitroimidazol-5-oyl)hydrazine (59)

A solution of 1-N-methyl-4-nitroimidazole-5-carbonyl chloride (19) (1.89 g; 0.01 mol) in dry dioxan (8.0 ml) was stirred and treated dropwise at room temperature with 100% hydrazine monohydrate (1.00 g, 0.02 mol). The mixture was stirred at room temperature for 1h then evaporated and the residue treated with water (10.0 ml). The resulting yellow solid was collected and crystallised to afford the 1,2-di-(1-N-methyl-4-nitroimidazol-5-oyl)hydrazine (59) (0.99 g; 60%) which formed colourless crystals, m.p. 301-303° (from ethanol-dimethylformamide), ν_{\max} 3140 (NH) and 1650 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 7.96 (2H, s, imidazole CH) and 3.78 (6H, s, imidazole CH_3).

Found: M^+ , 338.0710.

$\text{C}_{10}\text{H}_{10}\text{N}_8\text{O}_6$ requires: M , 338.0723.

The aqueous mother liquor was extracted with methylene chloride to give a low yield of an intractable solid which was not further investigated.

1-(1-N-Methyl-4-nitroimidazol-5-oyl)-2-toluene-p-sulphonyl-hydrazine (58)

A solution of toluene-p-sulphonylhydrazine (5.6 g, 0.03 mol) in glacial acetic acid (50.0 ml) was treated with fused sodium acetate (4.9 g, 0.06 mol) to give a slurry which was stirred magnetically and treated at room temperature in one portion with 1-N-methyl-4-nitroimidazole-5-carbonyl chloride (19) (5.6 g, 0.03 mol). The resulting suspension was stirred at room temperature for 3h, the resulting mixture evaporated and the solid residue treated with water (50.0 ml) to give a colourless solid which was washed with saturated aqueous sodium hydrogen carbonate, water and ethanol to give 1-(1-N-methyl-4-nitroimidazol-5-oyl)-2-toluene-p-sulphonylhydrazine (58) (8.9 g; 89%) which formed colourless crystals, m.p. 247-248° (from ethanol-dimethylformamide), ν_{\max} 3200 (NH), 1710 (CO) and 1510 and 1340 (NO_2) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 7.86 (1H, s, imidazole CH), 7.80 (2H, d, J8Hz, ArH), 7.38 (2H, d, J8Hz, ArH), 3.49 (3H, s, NCH_3) and 2.38 (3H, s, CH_3).

Found: C, 42.4; H, 3.9; N, 20.7%; M^+ , 339.

$\text{C}_{12}\text{H}_{13}\text{N}_5\text{O}_5\text{S}$ requires: C, 42.5; H, 3.9; N, 20.6%; M, 339.

The Attempted Base-catalysed Cyclisation of 1-(1-N-Methyl-4-nitroimidazol-5-oyl)-2-toluene-p-sulphonylhydrazine (58)

(i) Using piperidine as the base

A suspension of the imidazoloylhydrazine derivative (58) (0.68 g, 0.002 mol) in ethanol (50.0 ml) was heated under reflux, treated dropwise with piperidine (0.68 g, 0.008 mol) and the resulting yellow solution heated under reflux for 2.5h.

The mixture was evaporated to afford the piperidine salt of the imidazoloylhydrazine (58) (0.87 g; 100%) m.p. 138-143° (decomp.), ν_{\max} 3505 and 3400 br (NH), 1640 (CO), and 1500 and 1340 (NO₂) cm⁻¹. Treatment of this salt with dilute hydrochloric acid afforded the imidazoloylhydrazine (58), identified by comparison (i.r. and m.p.) with an authentic sample.

(ii) Using sodium ethoxide as the base

(a) A suspension of the imidazoloylhydrazine (58) (0.68 g, 0.002 mol) in absolute ethanol (10.0 ml) was heated under reflux and treated with a solution of sodium (0.10 g, 0.004 g.atom) in absolute ethanol (10.0 ml) and the mixture was heated under reflux for 1h. The resulting suspension was evaporated and the residue treated with water (5.0 ml) and extracted with methylene chloride (3x25.0 ml) to give an insignificant quantity of a gummy solid.

The aqueous mother liquor was acidified with concentrated hydrochloride acid to give the unreacted imidazoloylhydrazine (58) (0.63 g; 93%), m.p. 245-246°, identical (m.p. and i.r. spectrum) to an authentic sample.

(b) A suspension of the imidazoloylhydrazine (58) (1.7 g, 0.005 mol) in dry 1,2-dimethoxyethane (75.0 ml) was stirred and treated at room temperature with a solution of sodium (0.35 g, 0.015 g.atom) in absolute ethanol (50.0 ml). The resulting brown suspension was stirred at room temperature with protection from atmospheric moisture for 0.5h, then evaporated to give a brown solid which was powdered and heated under reflux with dry diethylene glycol-dimethyl ether (diglyme) (50.0 ml) for 1h. The resulting suspension was hot filtered

and the black solid residue dissolved in water (25.0 ml). This solution was acidified with concentrated hydrochloric acid to give the unreacted imidazoloylhydrazine (58) (1.7 g; 100%) m.p. 236-238°, identical (m.p. and i.r. spectrum) to an authentic sample.

(iii) Using potassium hydroxide as the base

(a) A solution of the imidazoloylhydrazine (58) (0.68 g, 0.002 mol) in ethanol (10.0 ml) was heated under reflux, treated with 20% w/v aqueous potassium hydroxide solution (5.0 ml), and the mixture heated under reflux for 1h. The resulting dark mixture was concentrated, treated with water (5.0 ml) and acidified with concentrated hydrochloric acid to give the unreacted imidazoloylhydrazine (58) (0.17 g; 25%) m.p. 233-235°, identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous mother liquor was extracted with methylene chloride (3x25.0 ml) to give a yellow solid (0.20 g) which was purified by sublimation under reduced pressure to give a product, m.p. 48-52°, tentatively formulated as the azo-imidazole-dicarboxylic acid (61).

Found: M^+ , 278.

$C_{10}H_{10}N_6O_4$ requires: M , 278.

(b) A solution of the imidazoloylhydrazine (58) (3.4 g, 0.01 mol) in ethanol (50.0 ml) was heated under reflux, treated with 20% w/v aqueous potassium hydroxide solution (25.0 ml), and the mixture heated under reflux for 3h. The resulting dark solution was concentrated and acidified with concentrated hydrochloric acid to give the unreacted imidazoloylhydrazine (58) (0.36 g; 11%) m.p. 228-232°, identical

(m.p. and i.r. spectrum) to an authentic sample.

The aqueous mother liquor was extracted with methylene chloride (3x50.0 ml) to afford a glassy solid (1.5 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture, which was not further investigated.

The aqueous mother liquor was neutralised using solid sodium acetate and extracted with methylene chloride (3x50.0 ml) to give an intractable brown oil (0.11 g) which was not further investigated.

1-N-Methyl-5-methylamino-4-nitroimidazole (75)

1-N-Methyl-5-methylamino-4-nitroimidazole (75) was prepared (yield 88%) by the reaction of 5-chloro-1-N-methyl-4-nitroimidazole (27) with 33% ethanolic methylamine as described by Schubert and Heydenhauss,⁷³ and had m.p. 145-149° (lit.,⁷³ 154-156°).

Cyanoacetyl Chloride⁷⁴

A solution of cyanoacetic acid (0.85 g, 0.01 mol) in dry ether (12.0 ml) was treated with phosphorus pentachloride (2.2 g, 0.01 mol) and the mixture stirred at room temperature with exclusion of atmospheric moisture for 45min. The solution was evaporated at room temperature under high vacuum (oil pump) to remove the phosphoryl chloride leaving cyanoacetyl chloride⁷⁴ as a golden yellow oil which was used immediately without purification.

The Attempted Reaction of 1-N-Methyl-5-methylamino-4-nitroimidazole (75) with Cyanoacetyl Chloride

A suspension of 1-N-methyl-5-methylamino-4-nitroimidazole (75) (1.6 g, 0.01 mol) in 1,2-dimethoxyethane (105 ml) was stirred and treated dropwise at room temperature with a solution of cyanoacetyl chloride (0.01 mol) in 1,2-dimethoxyethane (5.0 ml) and the mixture heated under reflux for 3h. The resulting suspension was hot filtered and the solid was combined with a second crop obtained from the filtrate on cooling to give the unreacted nitro-imidazole (75) (1.0 g; 65%), m.p. 157-159°, identical (m.p. and i.r. spectrum) to an authentic sample.

The 1,2-dimethoxyethane mother liquor was evaporated to give a low yield of an intractable brown gum which was not further investigated.

The Attempted Reaction of 1-N-Methyl-5-methylamino-4-nitroimidazole (75) with Cyanoacetic Acid

A stirred solution of 1-N-methyl-5-methylamino-4-nitroimidazole (75) (0.31 g, 0.002 mol) and cyanoacetic acid (0.17 g, 0.002 mol) in dry methylene chloride (50.0 ml) was treated dropwise at room temperature with a solution of dicyclohexylcarbodiimide (0.46 g, 0.0022 mol) in dry methylene chloride (10.0 ml) and the mixture stirred at room temperature for 1h. The resulting suspension was filtered to give dicyclohexylurea (0.15 g; 30%) m.p. 212-214° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The methylene chloride mother liquor was evaporated to

give a yellow-green solid (0.80 g) whose t.l.c. in ethanol over silica showed it to be a mixture of the unreacted nitro-imidazole (75) and dicyclohexylurea, which was not further investigated.

The Attempted Reaction of 1-N-Methyl-5-methylamino-4-nitro-imidazole (75) with Phenylacetyl Chloride

(a) A mixture of 1-N-methyl-5-methylamino-4-nitroimidazole (75) (0.79 g, 0.005 mol) and phenylacetyl chloride (5.0 ml) was heated under reflux for 1h. The resulting dark mixture was dissolved in methylene chloride and the solution washed with saturated aqueous sodium hydrogen carbonate solution (3x20.0 ml) and evaporated to give an oil. This was washed by decantation with ether and methanol then treated with aqueous 2M hydrochloric acid to give a solid (1.2 g) m.p. 142-150° whose t.l.c. in ethanol over silica showed it to be an unresolvable multicomponent mixture, which was not further investigated.

(b) A solution of 1-N-methyl-5-methylamino-4-nitroimidazole (75) (0.78 g, 0.005 mol) in glacial acetic acid (20.0 ml) was stirred at room temperature and treated with fused sodium acetate (0.83 g, 0.01 mol), then dropwise with phenylacetyl chloride (0.80 g, 0.005 mol) and the suspension stirred with protection from atmospheric moisture at room temperature for 3h. The resulting suspension was evaporated and the residue treated with water (10.0 ml) and extracted with methylene chloride (3x25.0 ml) to give a yellow solid. This was treated with saturated aqueous sodium hydrogen carbonate solution

(15.0 ml) and extracted with methylene chloride (3x25.0 ml) to give a yellow solid which was combined with a second crop obtained by bringing the aqueous mother liquor to a basic pH with aqueous 2M sodium hydroxide and extracting with methylene chloride (3x25.0 ml), to give the unreacted nitro-imidazole (75) (total 0.58 g; 74%) m.p. 135-140°, identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous sodium hydrogen carbonate mother liquor was acidified with concentrated hydrochloric acid to give phenylacetic acid (0.28 g; 41%) m.p. 67-69°, identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Reaction of 1-N-Methyl-5-methylamino-4-nitro-imidazole (75) with Ethoxalyl Chloride

(a) A solution of 1-N-methyl-5-methylamino-4-nitroimidazole (75) (0.78 g, 0.005 mol) in glacial acetic acid (10.0 ml) was stirred and treated at room temperature with fused sodium acetate (0.83 g, 0.01 mol) followed by ethoxalyl chloride (0.70 g, 0.005 mol) and the resulting suspension stirred with protection from atmospheric moisture at room temperature for 3h. The reaction mixture was then evaporated, the residue treated with water (10.0 ml) and the resulting solid collected and combined with a second crop obtained by extracting the aqueous mother liquor with methylene chloride (3x25.0 ml) and treating the solid obtained with saturated aqueous sodium hydrogen carbonate solution, to give the unreacted nitro-imidazole (75) (total 0.56 g; 72%), m.p. 144-147°, identical (m.p. and i.r. spectrum) to an authentic sample.

(b) A stirred solution of 1-N-methyl-5-methylamino-4-nitroimidazole (75) (0.78 g, 0.005 mol) in Analar pyridine (5.0 ml) was treated at room temperature with ethoxalyl chloride (0.69 g, 0.005 mol) and the resulting red solution stirred, with protection from atmospheric moisture, at room temperature for 1h. The mixture was poured into aqueous 2M hydrochloric acid (30.0 ml) and the solution acidified with concentrated hydrochloric acid and extracted with methylene chloride (3x50.0 ml) to give a gummy brown solid (0.93 g) whose t.l.c. in methylene chloride over alumina showed it to be a multicomponent mixture, containing the starting nitro-imidazole (75), which was not further investigated.

The aqueous mother liquor was neutralised with solid sodium acetate and extracted with methylene chloride to yield a yellow oil which was triturated with light petroleum to give the unreacted nitro-imidazole (75) (0.14 g; 18%) m.p. 80-85°, identical (i.r. spectrum) to an authentic sample.

1-N-Methyl-4-nitro-5-toluene-p-sulphonylamino-imidazole (87)

(a) A solution of toluene-p-sulphonamide (0.87 g, 0.005 mol) in absolute ethanol (15.0 ml) was mixed with a solution of sodium (0.13 g, 0.005 g.atom) in absolute ethanol (5.0 ml) followed by a solution of 5-chloro-1-N-methyl-4-nitroimidazole (27) (0.82, 0.005 mol) in absolute ethanol (20.0 ml) and the mixture heated under reflux for 1h. The resulting solution was evaporated and the residue treated with water (10.0 ml) to give unreacted toluene-p-sulphonamide (0.58 g; 66%) m.p. 105-108°, identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous filtrate was acidified with concentrated hydrochloric acid to give 1-N-methyl-4-nitro-5-toluene-p-sulphonylamino-imidazole (87) (0.58 g; 40%) m.p. 192-194° (decomp.) (lit.,⁷⁷ 210-211°).

(b) A solution of toluene-p-sulphonamide (17.12 g, 0.1 mol) in absolute ethanol (300 ml) was treated with a solution of sodium (2.53 g, 0.11 g.atom) in absolute ethanol (100 ml). The suspension was heated under reflux and treated with a solution of 5-chloro-1-N-methyl-4-nitroimidazole (27) (8.1 g, 0.05 mol) in absolute ethanol (450 ml) and the resulting yellow solution was heated under reflux for 3h. The mixture was evaporated and the residue treated with water (100 ml) to give unreacted toluene-p-sulphonamide (4.9 g; 29%) m.p. 128-131°, identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous mother liquor was acidified with concentrated hydrochloric acid, and the solid so obtained heated under reflux with ethanol (50.0 ml) for 15 min. and hot filtered to give 1-N-methyl-4-nitro-5-toluene-p-sulphonylamino-imidazole (87) (11.8 g; 80%) m.p. 198-200° (decomp.) (lit.,⁷⁷ 210-211°).

(c) A solution of toluene-p-sulphonamide (0.69 g, 0.004 mol) in dry dimethylformamide (2.0 ml) was added at room temperature to a stirred suspension of sodium hydride (0.12 g, 0.0048 mol) in dry dimethylformamide (1.0 ml) and the mixture stirred with protection from atmospheric moisture at room temperature for 15 min. A solution of 5-chloro-1-N-methyl-4-nitroimidazole (27) (0.65 g, 0.004 mol) in dry dimethylformamide (5.0 ml) was then added to the stirred suspension and the mixture heated under reflux for 3h. The resulting dark solution was treated with water (20.0 ml) and extracted

with methylene chloride (3x50.0 ml) to give a gummy solid (0.52 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture.

The aqueous mother liquor was acidified with concentrated hydrochloric acid to give 1-N-methyl-4-nitro-5-toluene-p-sulphonylamino-imidazole (87) (0.44 g; 37%) m.p. 194-197° (decomp.) (lit.,⁷⁷ 210-211°).

(d) A suspension of sodium hydride (0.06 g, 0.0022 mol) in dry dimethylformamide (2.0 ml) was treated with a solution of 5-amino-1-N-methyl-4-nitroimidazole (86) (0.29 g, 0.002 mol) in dry dimethylformamide (7.0 ml) and the mixture stirred, with protection from atmospheric moisture, at room temperature for 15 min. A solution of toluene-p-sulphonyl chloride (0.42 g, 0.0022 mol) in dry dimethylformamide (3.0 ml) was then added and the reaction mixture stirred at room temperature for 17h. Treatment with water (20.0 ml) afforded a solid which was combined with a second crop obtained by extracting the aqueous mother liquor with methylene chloride and triturating the resulting red oil with ethyl acetate, to give 1-N-methyl-4-nitro-5-toluene-p-sulphonylamino-imidazole (87) (total 0.27 g; 46%), m.p. 192-194°, identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous mother liquor was acidified with concentrated hydrochloric acid and extracted with methylene chloride to give a brown gummy solid which was triturated with toluene to afford unreacted nitro-imidazole (86) (0.01 g; 3%) m.p. 268-274° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

1-N-Methyl-4-nitro-5-(N-phenylacetyl,N-toluene-p-sulphonyl)
amino-imidazole (88a)

(a) A solution of 1-N-methyl-4-nitro-5-toluene-p-sulphonylamino-imidazole (87) (0.59 g, 0.002 mol) in 10% w/v aqueous sodium hydroxide (9.0 ml) was treated with phenylacetyl chloride (1.7 g, 0.011 mol) and the mixture shaken mechanically at room temperature for 2.5h. A further portion of 10% w/v aqueous sodium hydroxide (4.5 ml) was added, followed by further shaking for 0.5h. The resulting suspension was filtered to give 1-N-methyl-4-nitro-5-(N-phenylacetyl, N-toluene-p-sulphonyl)amino-imidazole (88a) (0.07 g; 8%) which formed colourless plates m.p. 211-213° (decomp.) (from toluene), ν_{\max} 1740 (CO) and 1510 and 1350 (NO₂) cm⁻¹, $\delta[(\text{CD}_3)_2\text{SO}]$ 8.11 (1H, s, imidazole CH), 7.81 (2H, d J8Hz, ArH), 7.43 (2H, d, J8Hz, ArH), 7.50-7.22 (3H, m, ArH), 7.04-6.92 (2H, m, ArH), 3.64 (1H, s, CH₂), 3.62 (1H, s, CH₂), 3.44 (3H, s, NCH₃) and 2.42 (3H, s, CH₃).

Found: C, 54.8; H, 4.3; N, 13.2%; M⁺, 414.

C₁₉H₁₈N₄O₅S requires: C, 55.1; H, 4.4; N, 13.5%; M, 414.

Workup of the aqueous mother liquor afforded no identifiable material.

(b) A solution of 1-N-methyl-4-nitro-5-toluene-p-sulphonylamino-imidazole (87) (0.74 g, 0.0025 mol) in dry dimethylformamide (5.0 ml) was added to a stirred suspension of sodium hydride (0.074 g, 0.003 mol) in dry dimethylformamide (2.0 ml) and the suspension stirred, with protection from atmospheric moisture, at room temperature for 15 min.

A solution of phenylacetyl chloride (0.47 g, 0.003 mol) in dry dimethylformamide (3.0 ml) was then added and the reaction mixture stirred at room temperature for 17h. The resulting solution was treated with water (20.0 ml) and the precipitated solid collected to give 1-N-methyl-4-nitro-5-(N-phenylacetyl,N-toluene-*p*-sulphonyl)amino-imidazole (88a) (0.80 g; 78%) m.p. 207-209° (decomp.) identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

The Attempted Base-catalysed Cyclisation of 1-N-Methyl-4-nitro-5-(N-phenylacetyl,N-toluene-*p*-sulphonyl)amino-imidazole (88a)

(i) Using potassium hydroxide-pyridine as the base

A solution of 1-N-methyl-4-nitro-5-(N-phenylacetyl,N-toluene-*p*-sulphonyl)amino-imidazole (88a) (0.62 g, 0.0015 mol) in Analar pyridine (2.0 ml) was treated with 20% w/v aqueous potassium hydroxide (2.0 ml) and the mixture stirred at 100° for 1h. The resulting solution was treated with water (5.0 ml) and acidified with aqueous 2M hydrochloric acid to give 1-N-methyl-4-nitro-5-toluene-*p*-sulphonylamino-imidazole (87) (0.19 g; 43%) m.p. 198-202° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The acidic aqueous phase was extracted with methylene chloride (3x50.0 ml) to give a yellow solid (0.37 g). This was treated with saturated aqueous sodium hydrogen carbonate solution and the resulting suspension filtered to give a small amount of toluene-*p*-sulphonamide, m.p. 125-129°, identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous sodium hydrogen carbonate mother liquor was

acidified with concentrated hydrochloric acid and extracted with methylene chloride (3x10.0 ml) to give a low yield of phenylacetic acid (0.02 g; 12%) m.p. 60-65°, identical (m.p. and i.r. spectrum) to an authentic sample.

(ii) Using triethylamine as the base

A solution of 1-N-methyl-4-nitro-5-(N-phenylacetyl,N-toluene-p-sulphonyl)amino-imidazole (88a) (0.42 g, 0.001 mol) in ethanol (30.0 ml) was heated under reflux and treated with triethylamine (0.56 ml; 0.004 mol) and the mixture heated under reflux for 6h. The resulting solution was evaporated to give a dark oil which was triturated with ethanol to afford 5-amino-1-N-methyl-4-nitroimidazole (86) (0.067 g; 47%) m.p. 285-290° (decomp.) (lit.,⁷⁸ 303°) identical (m.p. and i.r. spectrum) to an authentic sample.

The ethanolic mother liquor was evaporated to give a brown oil (0.50 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture.

5-(N-Cyanoacetyl,N-toluene-p-sulphonyl)amino-1-N-methyl-4-nitroimidazole (88b)

A vigorously stirred suspension of sodium hydride (0.06 g, 0.0025 mol) in dry dimethylformamide (2.0 ml) was treated with a solution of 1-N-methyl-4-nitro-5-toluene-p-sulphonyl-amino-imidazole (87) (0.74 g, 0.0025 mol) in dry dimethylformamide (5.0 ml) and the mixture stirred with protection from atmospheric moisture at room temperature for 0.5h. The resulting solution was evaporated and the residue dissolved

in dry 1,2-dimethoxyethane (5.0 ml). This solution was treated with cyanoacetyl chloride (0.005 mol) in dry 1,2-dimethoxyethane (4.0 ml) and stirred with protection from atmospheric moisture at room temperature for 16h. The resulting suspension was treated with water (10.0 ml) and the solid collected to give 5-(N-cyanoacetyl,N-toluene-p-sulphonyl)-amino-1-N-methyl-4-nitroimidazole (88b) (0.73 g; 74%) m.p. 177-180° (decomp.), ν_{\max} 1755 (CO) and 1510 and 1345 (NO_2) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 7.80 (1H, s, imidazole CH), 7.53 (2H, d, J8Hz, ArH), 7.32 (2H, d, J8Hz, ArH), 3.58 (3H, s, imidazole NCH_3), 3.44 (1H, s, CH_2), 3.24 (1H, s, CH_2) and 2.18 (3H, s, CH_3), which on attempted crystallisation gave the toluene-sulphonylamino-imidazole (87).

Found: ($\text{M}^+ - \text{COCHCN}$), 296.

$\text{C}_{14}\text{H}_{13}\text{N}_5\text{O}_5\text{S}$ requires: M, 363.

The aqueous mother liquor was extracted with methylene chloride (3x25.0 ml) to give a brown gum which was triturated with ether to afford the unreacted toluene-sulphonylamino-imidazole (87) (0.083 g; 11%) m.p. 195-196°, identical (m.p. and i.r. spectrum) to an authentic sample.

5-(N- α -Chloroacetyl,N-toluene-p-sulphonyl)amino-1-N-methyl-4-nitroimidazole (94)

A vigorously stirred suspension of sodium hydride (0.36 g, 0.015 mol) in dry dimethylformamide (2.0 ml) was treated with a solution of 1-N-methyl-4-nitro-5-toluene-p-sulphonylamino-imidazole (87) (3.70 g, 0.0125 mol) in dry dimethylformamide (10.0 ml) and the mixture stirred with protection from

atmospheric moisture at room temperature for 15 min. A solution of chloroacetyl chloride (2.85 g, 0.025 mol) in dry dimethylformamide (4.0 ml) was then added and the mixture stirred at room temperature for 16.5h. The resulting solution was treated with water (25.0 ml) to give 5-(N- α -chloroacetyl, N-toluene-*p*-sulphonyl)amino-1-N-methyl-4-nitroimidazole (94) (4.5 g; 97%) which formed colourless crystals m.p. 213-214° (decomp.) (from ethanol-dimethylformamide), ν_{\max} 1745 (CO) and 1510 and 1350 (NO₂) cm⁻¹, $\delta[(\text{CD}_3)_2\text{SO}]$ 8.14 (1H, s, imidazole CH), 7.81 (2H, d, J8Hz, ArH), 7.44 (2H, d, J8Hz, ArH), 4.42 (1H, s, CH₂), 4.33 (1H, s, CH₂), 3.38 (3H, s, imidazole NCH₃) and 2.42 (3H, s, CH₃).

Found: C, 42.0; H, 3.5; N, 14.8%; M⁺, 372/374.

C₁₃H₁₃ClN₄O₅S requires: C, 41.9; H, 3.5; N, 15.0%; M, 372/374.

The Attempted Reaction of 5-(N- α -Chloroacetyl,N-toluene-*p*-sulphonyl)amino-1-N-methyl-4-nitroimidazole (94) with Potassium Cyanide

A suspension of 5-(N- α -chloroacetyl-N-toluene-*p*-sulphonyl)-amino-1-N-methyl-4-nitroimidazole (94) (0.75 g, 0.002 mol) in ethanol (5.0 ml) was treated with a solution of potassium cyanide (0.40 g, 0.006 mol) in water (1.5 ml) and the resulting yellow suspension stirred at 30° for 45 min. After filtering the solid product was treated with aqueous 2M hydrochloric acid (5.0 ml) to give 1-N-methyl-4-nitro-5-toluene-*p*-sulphonylamino-imidazole (87) (0.45 g; 76%) m.p. 190-192°, identical (m.p. and i.r. spectrum) to an authentic sample.

Workup of the aqueous ethanolic mother liquor gave no further identifiable material.

The Attempted Reaction of 5-(N- α -Chloroacetyl,N-toluene-p-sulphonyl)amino-1-N-4-nitroimidazole (94) with Pyridine

A suspension of 5-(N- α -chloroacetyl,N-toluene-p-sulphonyl)-amino-1-N-methyl-4-nitroimidazole (94) (0.75 g, 0.002 mol) in Analar pyridine (4.0 ml) was heated gently to boiling for several min.. The resulting dark solution was allowed to cool and filtered to give a low yield of a gummy solid whose t.l.c. in ethanol over silica showed it to be an unresolvable multi-component mixture which was not further investigated.

The mother liquor was evaporated to give a dark oil which was triturated with methanol to afford 1-N-methyl-4-nitro-5-toluene-p-sulphonylamino-imidazole (87) (0.29 g; 50%) m.p. 200-203° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The methanolic mother liquor was evaporated to give a dark gum (0.40 g) whose t.l.c. in ethanol over silica showed it to be an unresolvable multicomponent mixture, which was not further investigated.

The Attempted Reaction of 5-(N- α -Chloroacetyl,N-toluene-p-sulphonyl)amino-1-N-methyl-4-nitroimidazole (94) with Sodium Benzenesulphinate

A solution of 5-(N- α -chloroacetyl,N-toluene-p-sulphonyl)amino-1-N-methyl-4-nitroimidazole (94) (0.75 g, 0.002 mol) and sodium benzenesulphinate (0.36 g, 0.0022 mol) in ethanol

(25.0 ml) was heated under reflux for 4h. The mixture was evaporated and the residue treated with water (5.0 ml) to give 1-N-methyl-4-nitro-5-toluene-p-sulphonylamino-imidazole (87) (0.52 g; 88%) m.p. 182-183° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous mother liquor was extracted with methylene chloride (3x10.0 ml) to give a yellow oil (0.18 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture, which was not further investigated.

5-(N-Ethoxalyl,N-toluene-p-sulphonyl)amino-1-N-methyl-4-nitroimidazole (102)

A vigorously stirred suspension of sodium hydride (0.29 g, 0.012 mol) in dry dimethylformamide (5.0 ml) was treated with a solution of 1-N-methyl-4-nitro-5-toluene-p-sulphonylamino-imidazole (87) (2.96 g, 0.01 mol) in dry dimethylformamide (10.0 ml) and the mixture was stirred with protection from atmospheric moisture at room temperature for 15 min. A solution of ethoxalyl chloride (1.37 g, 0.01 mol) in dry dimethylformamide (5.0 ml) was then added and the mixture stirred at room temperature for 16h. Treatment with water

(60.0 ml) afforded a solid, which was crystallised from ethanol to give 5-(N-ethoxalyl,N-toluene-p-sulphonyl)amino-1-N-methyl-4-nitroimidazole (102) (2.5 g; 62%) which formed colourless crystals m.p. 171-172° (from ethanol), ν_{\max} 1750-1720 br (CO) and 1510 and 1300 (NO₂) cm⁻¹, $\delta[(\text{CD}_3)_2\text{SO}]$ 8.20 (1H, s, imidazole CH), 7.86 (2H, d, J8Hz, ArH), 7.50 (2H, d, J8Hz, Ar), 4.10 (2H, q, J7Hz, CH₂), 3.80 (3H, s, NCH₃), 2.46 (3H, s, ArCH₃) and 1.01 (3H, t, J7Hz, CH₃).

Found: C, 45.5; H, 4.0; N, 14.1%; M⁺, 396.

C₁₅H₁₆N₄O₇S requires: C, 45.5; H, 4.1; N, 14.1%; M, 396.

The aqueous dimethylformamide mother liquor was extracted with methylene chloride (2x100 ml) to give the unreacted toluene-p-sulphonylamino-imidazole (87) (0.058 g; 2%) m.p. 198-200° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the ethanolic filtrate gave an orange solid (0.27 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture, which was not further investigated.

The Attempted Reductive Cyclisation of 5-(N-Ethoxalyl,N-toluene-p-sulphonyl)amino-1-N-methyl-4-nitroimidazole (102)

(a) A solution of 5-(N-ethoxalyl,N-toluene-p-sulphonyl)-amino-1-N-methyl-4-nitroimidazole (102) (0.40 g, 0.001 mol)

in ethanol (100 ml) was hydrogenated over 10% palladium-on-charcoal (0.14 g) at room temperature and atmospheric pressure for 3h. No hydrogen was absorbed. The reaction mixture was filtered through kieselguhr and the filtrate evaporated to give a brown oil which on trituration with ether afforded a gummy solid. This was crystallised from ethanol to give 1-N-methyl-4-nitro-5-toluene-p-sulphonylamino-imidazole (87) (0.14 g; 47%) m.p. 201-204° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The combined ethereal and ethanolic filtrates were evaporated to give gums whose t.l.c. in ethyl acetate over silica showed them to be unresolvable multicomponent mixtures, which were not further investigated.

(b) A solution of 5-(N-ethoxalyl,N-toluene-p-sulphonyl)-amino-1-N-methyl-4-nitroimidazole (102) (2.0 g, 0.005 mol) in dioxane (50.0 ml) was treated with 2% w/v aqueous sodium hydroxide solution (5.0 ml). This mixture was stirred mechanically under nitrogen and 10% palladium-on-charcoal catalyst (0.02 g) added, followed by addition of a solution of sodium borohydride (0.38 g, 0.01 mol) in water (5.0 ml) over 10 min. The resulting mixture was stirred under nitrogen at room temperature for 15 min, then filtered through a celite pad, which was washed with water and dioxane. The combined aqueous dioxane filtrate and washings were treated with water (5.0 ml) to give a solid which was combined with a second crop obtained by acidifying the aqueous filtrate with concentrated hydrochloric acid to give 1-N-methyl-4-nitro-5-toluene-p-sulphonylamino-imidazole (87) (1.3 g; 86%) m.p. 194-197° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

1-N-Methyl-4-nitro-5-(N-phenacyl,N-toluene-p-sulphonyl)-
amino-imidazole (106)

A vigorously stirred suspension of sodium hydride (0.29 g, 0.012 mol) in dry dimethylformamide (4.0 ml) was treated with a solution of 1-N-methyl-4-nitro-5-toluene-p-sulphonyl-amino-imidazole (87) (3.0 g, 0.01 mol) in dry dimethylformamide (10.0 ml) and the mixture stirred with protection from atmospheric moisture at room temperature for 15 min. A solution of 2-bromoacetophenone (4.0 g, 0.02 mol) in dry dimethylformamide (4.0 ml) was then added and the reaction mixture stirred at room temperature for 16h. The resulting solution was then treated with water (50.0 ml) and the solid obtained crystallised from ethanol-dimethylformamide to give 1-N-methyl-4-nitro-5-(N-phenacyl,N-toluene-p-sulphonyl)amino-imidazole (106) (2.9 g; 69%) which formed colourless crystals m.p. 182-183° (from ethanol-dimethylformamide), ν_{\max} 1705 (CO) and 1505 and 1340 (NO₂) cm⁻¹, δ [(CD₃)₂SO] 8.00-7.32 (10H, m, ArH and imidazole CH), 5.58 (1H, d, J18Hz, CH₂), 5.05 (1H, d, J18Hz, CH₂), 3.98 (3H, s, imidazole NCH₃) and 2.40 (3H, s, CH₃).

Found: C, 55.1; H, 4.4; N, 13.4%; M⁺, 414.

C₁₉H₁₈N₄O₅S requires: C, 55.1; H, 4.4; N, 13.5%; M, 414.

Workup of the ethanolic filtrate gave a brown gum (2.23 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture, which was not further investigated.

The Attempted Reductive Cyclisation of 1-N-Methyl-4-nitro-5-(N-phenacyl,N-toluene-p-sulphonyl)amino-imidazole (106)

A solution of 1-N-methyl-4-nitro-5-(N-phenacyl,N-toluene-p-sulphonyl)amino-imidazole (106) (0.41 g, 0.001 mol) in ethanol (100 ml) was hydrogenated over palladium-on-charcoal (0.04 g) at room temperature and atmospheric pressure for 4h. Hydrogen was absorbed. The reaction mixture was filtered through kieselguhr and the filtrate evaporated to give a brown oil (0.23 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture.

5-Amino-1-N-methyl-4-nitroimidazole (86)

A suspension of 5-chloro-1-N-methyl-4-nitroimidazole (27) (8.0 g, 0.05 mol) in liquid ammonia (100 ml) was sealed in an autoclave for 72h. The resulting suspension was allowed to evaporate, the residue treated with water (20.0 ml) and the mixture filtered to give 5-amino-1-N-methyl-4-nitroimidazole (86) (6.8 g; 97%) m.p. 292-294° (decomp.) (lit.,⁷⁸ 303°).

Found: M^+ , 142.

Calc. for $C_4H_6N_4O_2$: M, 142.

1-N-Methyl-4-nitro-5-(N-phenylacetyl)amino-imidazole (113)

A vigorously stirred suspension of sodium hydride (0.29 g, 0.012 mol) in dry dimethylformamide (2.0 ml) was treated with a suspension of 5-amino-1-N-methyl-4-nitroimidazole (86) (1.4 g, 0.01 mol) in dry dimethylformamide (10.0 ml) and the mixture stirred with protection from atmospheric moisture at room temperature for 1h. This mixture was then treated with

a solution of phenylacetyl chloride (2.3 g, 0.015 mol) in dry dimethylformamide (2.0 ml) and stirred at room temperature for 18.5h. The resulting green suspension was treated with water (25.0 ml) and methylene chloride (50.0 ml) and the three-phase system filtered to give the unreacted amino-nitro-imidazole (86) (0.22 g; 16%) m.p. 289-290° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous mother liquor was extracted with methylene chloride (2x50.0 ml) and the combined organic phases were evaporated to give a solid which was washed with saturated aqueous sodium hydrogen carbonate, water, and dried to give 1-N-methyl-4-nitro-5-(N-phenylacetyl)amino-imidazole (113) (1.6 g; 69%) which formed yellow crystals m.p. 187-188° (from ethanol-dimethylformamide), ν_{\max} 1680 (CO) and 1500 and 1340 (NO₂) cm⁻¹, $\delta[(\text{CD}_3)_2\text{SO}]$ 10.65 (1H, s, NH), 7.75 (1H, s, imidazole CH), 7.30 (5H, s, ArH), 3.76 (3H, s, imidazole NCH₃) and 3.54 (2H, s, CH₂).

Found: C, 55.2; H, 4.8; N, 21.5%; M^+ , 260.

C₁₂H₁₂N₄O₃ requires: C, 55.4; H, 4.6; N, 21.5%; M , 260.

The aqueous sodium hydrogen carbonate washings were acidified with aqueous 2M hydrochloric acid and extracted with methylene chloride (3x50.0 ml) to give phenylacetic acid (0.27 g; 13%) m.p. 74-75°, identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Base-catalysed Cyclisation of 1-N-Methyl-4-nitro-5-(N-phenylacetyl)amino-imidazole (113)

A solution of 1-N-methyl-4-nitro-5-(N-phenylacetyl)amino-

imidazole (113) (0.52 g, 0.002 mol) in Analar pyridine (2.5 ml) was treated with 20% w/v aqueous potassium hydroxide solution (2.5 ml) and the mixture stirred at 100° for 1h. The resulting solution was diluted with water (5.0 ml) and acidified with concentrated hydrochloric acid, then extracted with ethyl acetate (3x50.0 ml) to give a brown oil. This was triturated with light petroleum-ethanol to yield a dark gummy solid which was washed with saturated aqueous sodium hydrogen carbonate solution, water, and dried to afford the unreacted phenylacetylamino-imidazole (113) (0.20 g; 38%) m.p. 145-150° (decomp.) identical (i.r. spectrum) to an authentic sample.

The light-petroleum-ethanol mother liquor was evaporated to give a red oil (0.16 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture, which was not further investigated.

The Attempted Reaction of 5-Amino-1-N-methyl-4-nitroimidazole (86) with Cyanoacetyl Chloride

A vigorously stirred suspension of sodium hydride (0.05 g, 0.002 mol) in dry dimethylformamide (2.0 ml) was treated with a suspension of 5-amino-1-N-methyl-4-nitroimidazole (86) (0.28 g, 0.002 mol) in dry dimethylformamide (5.0 ml) and the mixture stirred with protection from atmospheric moisture at room temperature for 1h. After solvent removal at reduced pressure the residue was suspended in dry 1,2-dimethoxyethane (2.0 ml), treated with a solution of cyanoacetyl chloride⁷⁴ (0.004 mol) in dry 1,2-dimethoxyethane (2.0 ml),

and the mixture stirred at room temperature for 16h. The resulting suspension was treated with water (5.0 ml) and the solid obtained washed with saturated aqueous sodium hydrogen carbonate solution, water, and dried to give the unreacted amino-nitroimidazole (86) (0.28 g; 100%) m.p. 288-290° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Dicyclohexylcarbodiimide-catalysed Condensation of 5-Amino-1-N-methyl-4-nitroimidazole (86) with Cyanoacetic Acid

A warm solution of 5-amino-1-N-methyl-4-nitroimidazole (86) (0.28 g, 0.002 mol) in dry dimethylformamide (25.0 ml) was treated with cyanoacetic acid (0.18 g, 0.002 mol) followed by a solution of dicyclohexylcarbodiimide (0.45 g, 0.0022 mol) in dry dimethylformamide (5.0 ml) and the mixture stirred with protection from atmospheric moisture at room temperature for 4h. The resulting suspension was filtered, the solid treated with aqueous 2M sodium hydroxide (5.0 ml) and refiltered to give 1,3-dicyclohexylurea (0.38 g; 77%) m.p. 226-228°, identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous alkaline filtrate was acidified with concentrated hydrochloric acid to give a solid which was combined with a second crop obtained by evaporating the dimethylformamide mother liquor and treating the residue obtained with ether, to give the unreacted amino-nitro-imidazole (86) (0.28 g; 100%) m.p. 285-290° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

5-(N-Chloroacetyl)amino-1-N-methyl-4-nitroimidazole (115)

A vigorously stirred suspension of sodium hydride (0.06 g, 0.0022 mol) in dry dimethylformamide (2.0 ml) was treated with a suspension of 5-amino-1-N-methyl-4-nitroimidazole (86) (0.29 g, 0.002 mol) in dry dimethylformamide (6.0 ml) and the mixture stirred with protection from atmospheric moisture at room temperature for 1h. A solution of chloroacetyl chloride (0.26 g, 0.0022 mol) in dry dimethylformamide (2.0 ml) was added and the mixture stirred at room temperature for 16h. After addition of water (10.0 ml), solid was collected which was shown to be the unreacted amino-nitro-imidazole (86) (0.11 g; 38%) m.p. 290-291° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous mother liquor was extracted with methylene chloride to give a gummy solid which solidified on contact with methylene chloride-light petroleum to afford 5-(N-chloroacetyl)-amino-1-N-methyl-4-nitroimidazole (115) (0.20 g; 46%) which formed light brown needles m.p. 188-189° (from glacial acetic acid), ν_{\max} 1710 (CO), 1500 and 1350 (NO₂) cm⁻¹, $\delta[(\text{CD}_3)_2\text{SO}]$ 10.80 (1H, br, s, NH), 7.80 (1H, s, imidazole CH), 4.41 (2H, s, CH₂) and 3.53 (3H, s, imidazole NCH₃).

Found: M⁺, 218.0203.

C₆H₇³⁵ClN₄O requires: M, 218.0207.

Found: M⁺, 220.0171.

C₆H₇³⁷ClN₄O₃ requires: M, 220.0177.

The Attempted Reaction of 5-(N-Chloroacetyl)amino-1-N-methyl-4-nitroimidazole (115) with Potassium Cyanide

A suspension of 5-(N-chloroacetyl)amino-1-N-methyl-4-nitroimidazole (115) (0.44 g, 0.002 mol) in ethanol (5.0 ml) was treated with a solution of potassium cyanide (0.40 g, 0.006 mol) in water (1.5 ml) and the red-brown solution stirred at 30° for 45 min. The mixture was then treated with water and animal charcoal and filtered through kieselguhr. The filtrate was acidified with aqueous 2M sulphuric acid and filtered to remove inorganic material. The dark filtrate was extracted with methylene chloride to give a three phase system which was filtered and the solid combined with further material obtained by evaporating the methylene chloride extract to give the unreacted chloroacetyl-amino-imidazole (115) (0.32 g; 74%) m.p. 180-182° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Reaction of 5-Amino-1-N-methyl-4-nitroimidazole (86) with 2-Bromoacetophenone

A vigorously stirred suspension of sodium hydride (0.06 g, 0.0022 mol) in dry dimethylformamide (2.0 ml) was treated with a suspension of 5-amino-1-N-methyl-4-nitroimidazole (86) (0.29 g, 0.002 mol) in dry dimethylformamide (5.0 ml) and the mixture stirred with protection from atmospheric moisture at room temperature for 1h. The mixture was then treated with a solution of 2-bromoacetophenone (0.45 g, 0.0022 mol) in dry dimethylformamide (2.0 ml) and stirred at room temperature for 17h. The resulting dark mixture was treated with water

(20.0 ml) and the solid collected to give the unreacted amino-nitro-imidazole (86) (0.22 g; 76%) m.p. 277° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

Extraction of the aqueous mother liquor with ethyl acetate gave only an intractable brown oil.

The Attempted Acid-catalysed Hydrolysis of 1-N-Methyl-4-nitro-5-(N-phenacyl,N-toluene-p-sulphonyl)amino-imidazole (88a)

A solution of 1-N-methyl-4-nitro-5-(N-phenacyl,N-toluene-p-sulphonyl)amino-imidazole (88a) (0.83 g, 0.002 mol) in glacial acetic acid (5.0 ml) and concentrated sulphuric acid (5.0 ml) was heated at 100° for 1h. The resulting dark solution was treated with ice (30.0 g) and filtered to remove a small amount of an uncharacterised brown solid.

The aqueous mother liquor was extracted with methylene chloride to give a brown oil (0.24 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multi-component mixture, which was not further investigated.

The Attempted Reaction of 5-Chloro-1-N-methyl-4-nitroimidazole (27) with Ethoxycarbonylacetamidine Hydrochloride

(a) A solution of ethoxycarbonylacetamidine hydrochloride⁸⁶ (0.67 g, 0.004 mol) in dry dimethylformamide (5.0 ml) was stirred and treated dropwise at 0-10° (ice-water bath) with triethylamine (1.6 g, 0.016 mol). After stirring for 5 min a solution of 5-chloro-1-N-methyl-4-nitroimidazole (27) (0.65 g, 0.004 mol) in dry dimethylformamide (5.0 ml) was added dropwise and the resulting mixture stirred at

room temperature for 21.5h. Addition of water (10.0 ml), followed by extraction with methylene chloride (3x25.0 ml), afforded a yellow gummy solid which was triturated with ether and crystallised from ethanol to give the unreacted chloro-nitroimidazole (27) (0.4 g; 60%) m.p. 142-143°, identical (m.p. and i.r. spectrum) to an authentic sample.

Workup of the combined ether and ethanolic mother liquors gave gums whose t.l.c. in ethyl acetate over silica showed them to be unresolvable multicomponent mixtures, which were not further investigated.

(b) Triethylamine (1.6 g, 0.016 mol) was added dropwise to a solution of ethoxycarbonylacetamidine hydrochloride⁸⁶ (0.99 g, 0.006 mol) in ethanol (25.0 ml) and the resulting solution treated with a warm solution of 5-chloro-1-N-methyl-4-nitroimidazole (27) (0.65 g, 0.004 mol) in ethanol (50.0 ml). This mixture was heated under reflux for 6h. The resulting suspension was evaporated and the residue treated with water (5.0 ml) and filtered to give a solid. This was combined with a second crop obtained by extracting the aqueous mother liquor with methylene chloride and triturating the material obtained with toluene-light petroleum, to give the unreacted chloro-nitroimidazole (27) (0.59 g; 90%) m.p. 143-145°, identical (m.p. and i.r. spectrum) to an authentic sample.

Dipotassium Nitrodithioacetate (152)

Dipotassium nitrodithioacetate (152) was prepared (yield 71%) by the reaction of nitromethane with carbon disulphide in the presence of aqueous potassium hydroxide as described

by Freund⁹³ and had m.p. 207-208° (lit.,⁹³ 203.5°).

1-Nitro-2,2-bis-methylthioethene (153)

1-Nitro-2,2-bis-methylthioethene (153) was prepared (yield 59%) by the reaction of dipotassium nitrodithioacetate (152) with dimethyl sulphate as described by Gompper and Schaefer⁹² and had m.p. 118-121° (lit.,⁹² 125-126°).

2-Benzylamino-2-methylthio-1-nitroethene (155)

2-Benzylamino-2-methylthio-1-nitroethene (155) was prepared (yield 85%) by the reaction of 1-nitro-2,2-bis-methylthioethene (153) with benzylamine as described by Sone *et al.*,⁹⁴ and had m.p. 94-97° (lit.,⁹⁴ 108°).

2-Benzylamino-2-hydrazino-1-nitroethene (154)

2-Benzylamino-2-hydrazino-1-nitroethene (154) was prepared (yield 72%) by the reaction of 2-benzylamino-2-methylthio-1-nitroethene (155) with 100% hydrazine monohydrate as described by Hamberger *et al.*⁹⁰ and had m.p. 155° (decomp.) (lit.,⁹⁰ 155-157°).

3-Benzylamino-4-nitropyridazine (156)

A mixture of 2-benzylamino-2-hydrazino-1-nitroethene (154) (1.1 g, 0.005 mol) and 40% aqueous glyoxal (7.5 ml, 0.05 mol) in water (100 ml) and benzene (100 ml) was treated with a 40% w/w aqueous benzyltrimethylammonium hydroxide solution (2.0 ml) and the mixture stirred vigorously at room temperature for 18h. The resulting three phase system was

filtered to give the unreacted hydrazino-ethene (154) (0.27 g; 26%) identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The aqueous phase was separated and extracted with methylene chloride and the combined methylene chloride and benzene extracts evaporated to give a gummy solid which was triturated with light petroleum to afford 3-benzylamino-4-nitropyridazine (156) (0.59 g; 51%) which formed brown crystals m.p. 161-162° (from ethanol) (lit.,⁹⁰ 157-160°), ν_{\max} 3420 (NH) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.80 (1H, d, J4Hz, pyridazine H-5), 8.70 (1H, br, s, NH), 8.07 (1H, d, J4Hz, pyridazine H-6), 7.40-7.20 (5H, m, ArH) and 4.90 (2H, d, J4Hz, CH_2).

Found: M^+ , 230.

Calc. for $\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}_2$: M, 230.

The Attempted Base-catalysed Cyclisation of 3-Benzylamino-4-nitropyridazine (156)

3-Benzylamino-4-nitropyridazine (156) (0.46 g, 0.002 mol) was added to a solution of potassium hydroxide (0.40 g, 0.01 mol) in methanol (8.0 ml) and the mixture heated under reflux for 5h. The resulting suspension obtained was evaporated and the residue treated with water (10.0 ml) and extracted with ethyl acetate to give a gummy red solid (0.1 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture, which was not further investigated.

The aqueous mother liquor was acidified with concentrated hydrochloric acid and extracted with ethyl acetate to give a

brown gummy solid (0.06 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture from which no identifiable material could be obtained.

2-Hydrazino-2-methylthio-1-nitroethene (158)

2-Hydrazino-2-methylthio-1-nitroethene (158) was prepared (yield 95%) by the reaction of 1-nitro-2,2-bis-methylthioethene (153) with 100% hydrazine monohydrate as described by Hamberger et al.⁹⁰ and was obtained as a brown oil which was used without further purification.

3-Methylthio-4-nitropyridazine (159)

(a) A mixture of 2-hydrazino-2-methylthio-1-nitroethene (158) (3.1 g, 0.02 mol) and 40% aqueous glyoxal (30 ml, 0.02 mol) in water (200 ml) and benzene (400 ml) was treated with 40% w/w aqueous benzyltrimethylammonium hydroxide solution (8.0 ml) and the mixture was stirred vigorously at room temperature for 17h. An intractable gummy solid was removed by filtration and the aqueous phase separated and extracted with benzene. Evaporation of the combined benzene extracts gave a brown solid which was subjected to dry column chromatography over alumina.

Elution with ether afforded 3-methylthio-4-nitropyridazine (159) (1.6 g; 48%) m.p. 86-88° (lit.,⁹⁰ 117-120°) ν_{\max} 1520 and 1350 (NO₂) cm⁻¹, δ_{H} [(CD₃)₂SO] 9.47 (1H, d, J6Hz, pyridazine H-5), 8.37 (1H, d, J6Hz, pyridazine H-6) and 2.74 (3H, s, SCH₃), δ_{C} [(CD₃)₂SO] 156.39 (C-NO₂), 149.31 (CH), 144.39 (C-SCH₃), 120.67 (CH) and 114.01 (CH₃S).

Found: M^+ , 171.

Calc. for $C_5H_5N_3O_2S$: M , 171.

(b) A solution of 40% aqueous glyoxal (1.2 g, 0.008 mol) and sodium carbonate (0.85 g, 0.008 mol) in water (20.0 ml) was treated dropwise over a 10 min period, with stirring at 8° (ice-water bath) with a solution of 2-hydrazino-2-methylthio-1-nitroethene (158) (1.20 g, 0.008 mol) in ethanol (4.0 ml). After stirring at 8° for 45 min the suspension was filtered to give 3-methylthio-4-nitropyridazine (159) (0.24 g; 17%) m.p. 90-95° (decomp.) (lit.,⁹⁰ 117-120°), identical (i.r. spectrum) to a sample prepared in (a) before.

The Attempted Reaction of 3-Methylthio-4-nitropyridazine (159) with Hydrazine Monohydrate

(a) A solution of 3-methylthio-4-nitropyridazine (159) (0.34 g, 0.002 mol) and 100% hydrazine monohydrate (0.11 g, 0.002 mol) in ethanol (10.0 ml) was heated under reflux for 1h. The mixture was evaporated to give a dark gum (0.34 g) whose t.l.c. in ether over silica showed it to be an unresolvable multicomponent mixture, which was not further investigated.

(b) A solution of 3-methylthio-4-nitropyridazine (159) (0.17 g, 0.001 mol) and 100% hydrazine monohydrate (0.07 g, 0.001 mol) in ethanol (10.0 ml) was stirred at room temperature for 19h. Evaporation of the solution gave a brown gum (0.16 g) whose t.l.c. in ether over silica showed it to be an unresolvable multicomponent mixture, which was not further investigated.

The Attempted Reaction of 3-Methylthio-4-nitropyridazine
(159) with Phenylhydrazine

A solution of 3-methylthio-4-nitropyridazine (159) (0.36 g, 0.002 mol) in dry benzene (25.0 ml) was treated with a solution of phenylhydrazine (0.24 g, 0.002 mol) in dry benzene (5.0 ml) and the mixture stirred at room temperature for 18h, then heated under reflux for 4h. The solution obtained was evaporated to give a brown gum which was treated with aqueous 2M hydrochloric acid (10.0 ml) and extracted with methylene chloride to give a brown oil (0.19 g) whose t.l.c. in ether over silica showed it to be an unresolvable mixture from which no identifiable material was obtained.

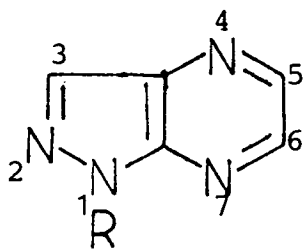
The aqueous phase was neutralised with solid sodium acetate and extracted with methylene chloride to give a brown gum (0.24 g) whose t.l.c. in ether over silica showed it to be an unresolvable mixture, which was not further investigated.

The Attempted Oxidation of 3-Methylthio-4-nitropyridazine
(159) with Hydrogen Peroxide

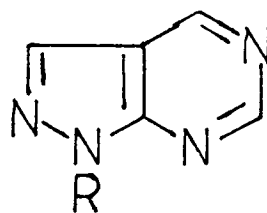
A solution of 3-methylthio-4-nitropyridazine (159) (0.35 g, 0.002 mol) in glacial acetic acid (5.0 ml) was treated with 30% aqueous hydrogen peroxide (2.5 ml) and the mixture stirred at 50° for 19h. The mixture was neutralised with solid sodium acetate, then extracted with methylene chloride (50.0 ml) and ethyl acetate (2x50.0 ml) to give a yellow oil (0.14 g) from which no identifiable material could be obtained.

CHAPTER THREE

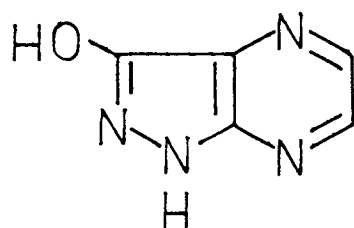
Studies on the Synthesis of N-Oxygenated Pyrazolo[3,4-b]pyrazines and Their Aza- analogues



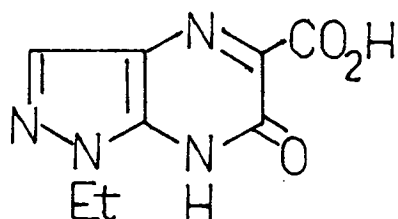
(1)



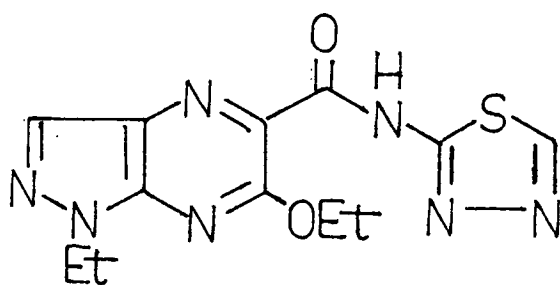
(2)



(3)

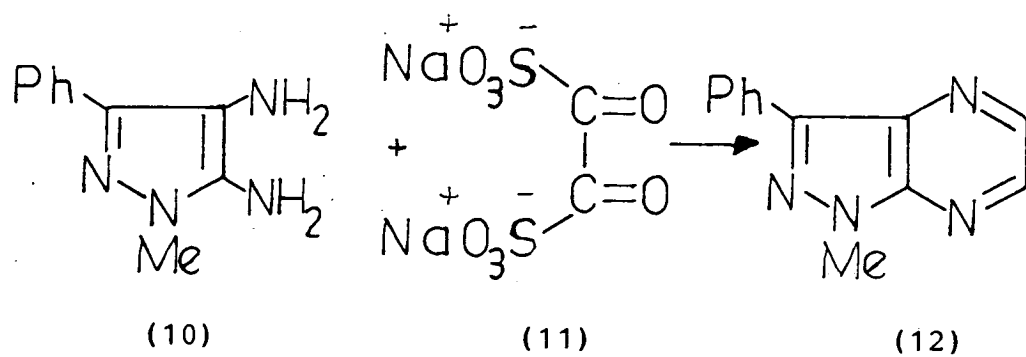
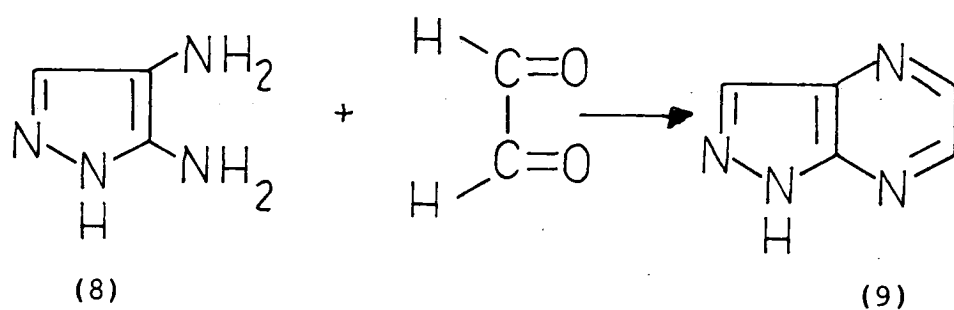
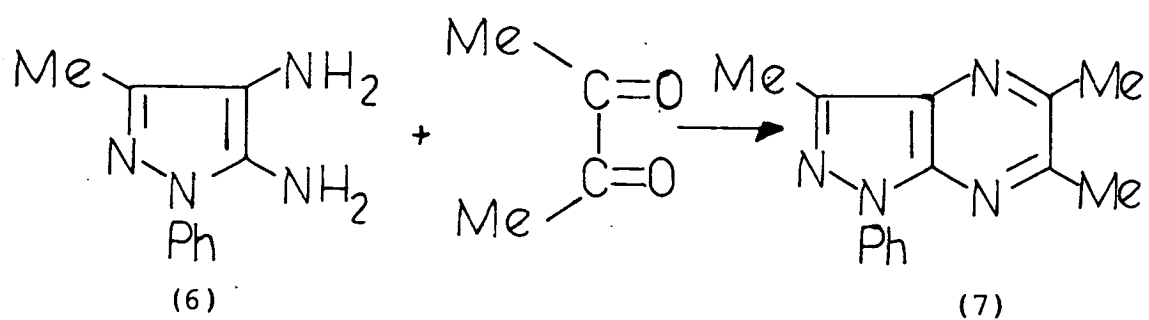


(4)



(5)

Scheme 1



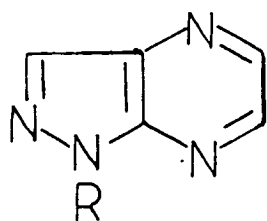
Scheme 2

Studies on the Synthesis of N-Oxygenated Pyrazolo[3,4-b]-pyrazines and Their Aza-analogues

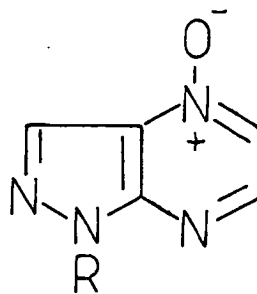
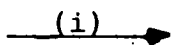
Derivatives (Scheme 1) of the pyrazolo[3,4-b]pyrazine ring system (1) which are isosteric and isomeric with derivatives of the imidazo[4,5-d]pyrimidine (purine) ring system (2) are of interest because of their potential biological activity. The hypoxanthine analogue (3) is a possible purine antimetabolite,⁹⁸ while Hoehn⁹⁹ has reported anti-inflammatory, tranquilizing and antiasthmatic activity for pyrazolo[3,4-b]pyrazine derivatives of the types (4) and (5).

Pyrazolo[3,4-b]pyrazine derivatives are readily synthesised (Scheme 2) by the condensation of 3,4-diaminopyrazoles with 1,2-dicarbonyl compounds.^{98,100-103} Pyrazolo[3,4-b]pyrazine synthesis of this type is exemplified (Scheme 2) by Grandberg and Klychko's reaction of 4,5-diamino-3-methyl-1-phenylpyrazole (6) with diacetyl to give 1-phenyl-3,5,6-trimethylpyrazolo[3,4-b]pyrazine (7).¹⁰¹ The parent pyrazolo[3,4-b]pyrazine (9) was later reported by Biffin, Brown and Porter,¹⁰⁰ as the product of the reaction of 4,5-diaminopyrazole (8) with glyoxal. In closely related processes (Scheme 2) 4,5-diaminopyrazoles (10) react readily with the glyoxal sodium bisulphite complex (11) to afford 5,6-unsubstituted pyrazolo[3,4-b]pyrazines (12).¹⁰²

In contrast to the ready accessibility of simple pyrazolo[3,4-b]pyrazine derivatives, N-oxygenated pyrazolo[3,4-b]pyrazines appear to have been rarely investigated, with only two papers reported in the literature to date. The direct oxidation (Scheme 3) of pyrazolo[3,4-b]pyrazines (13)

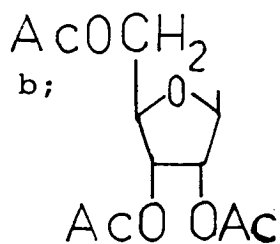


(13)



(14)

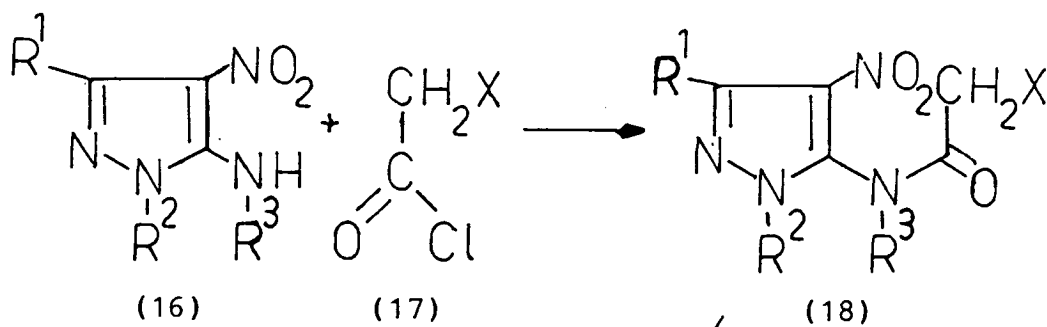
a; $\frac{R}{H}$



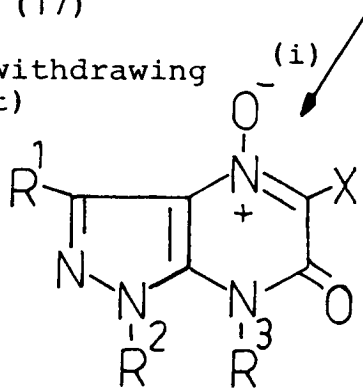
(15)

(i) H_2O_2 .

Scheme 3



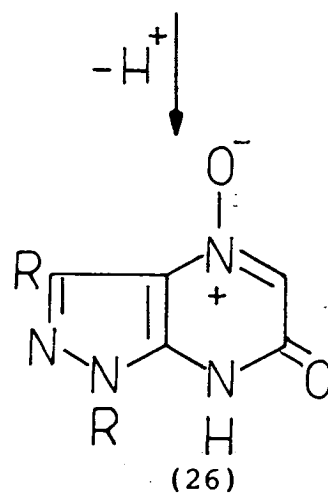
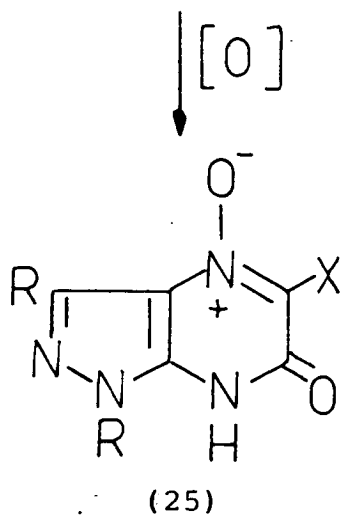
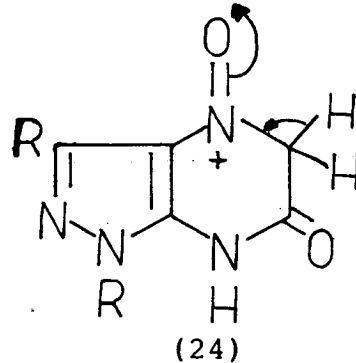
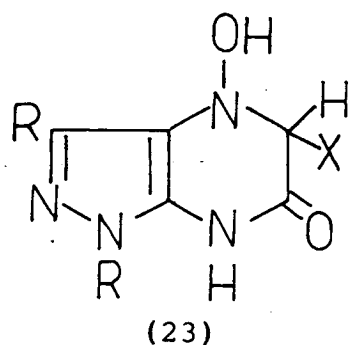
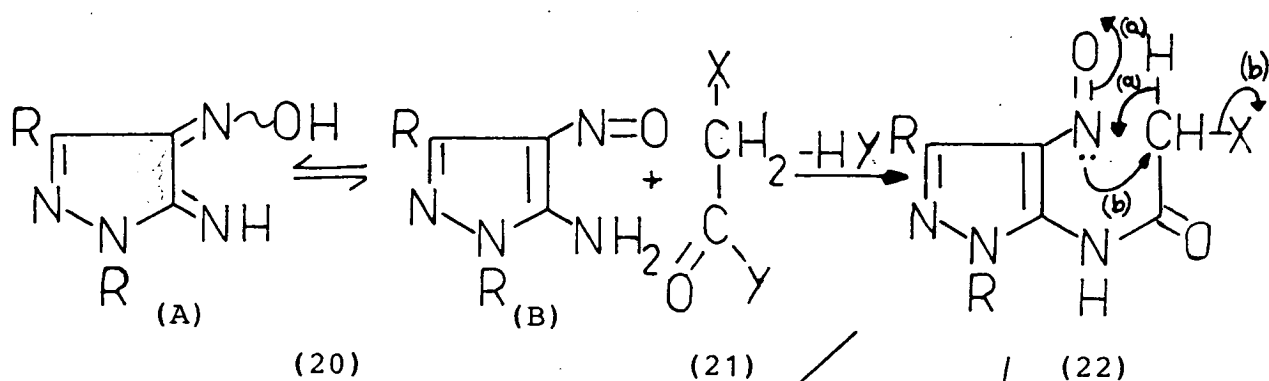
(X = an electron-withdrawing substituent)



(19)

(i) base.

Scheme 4



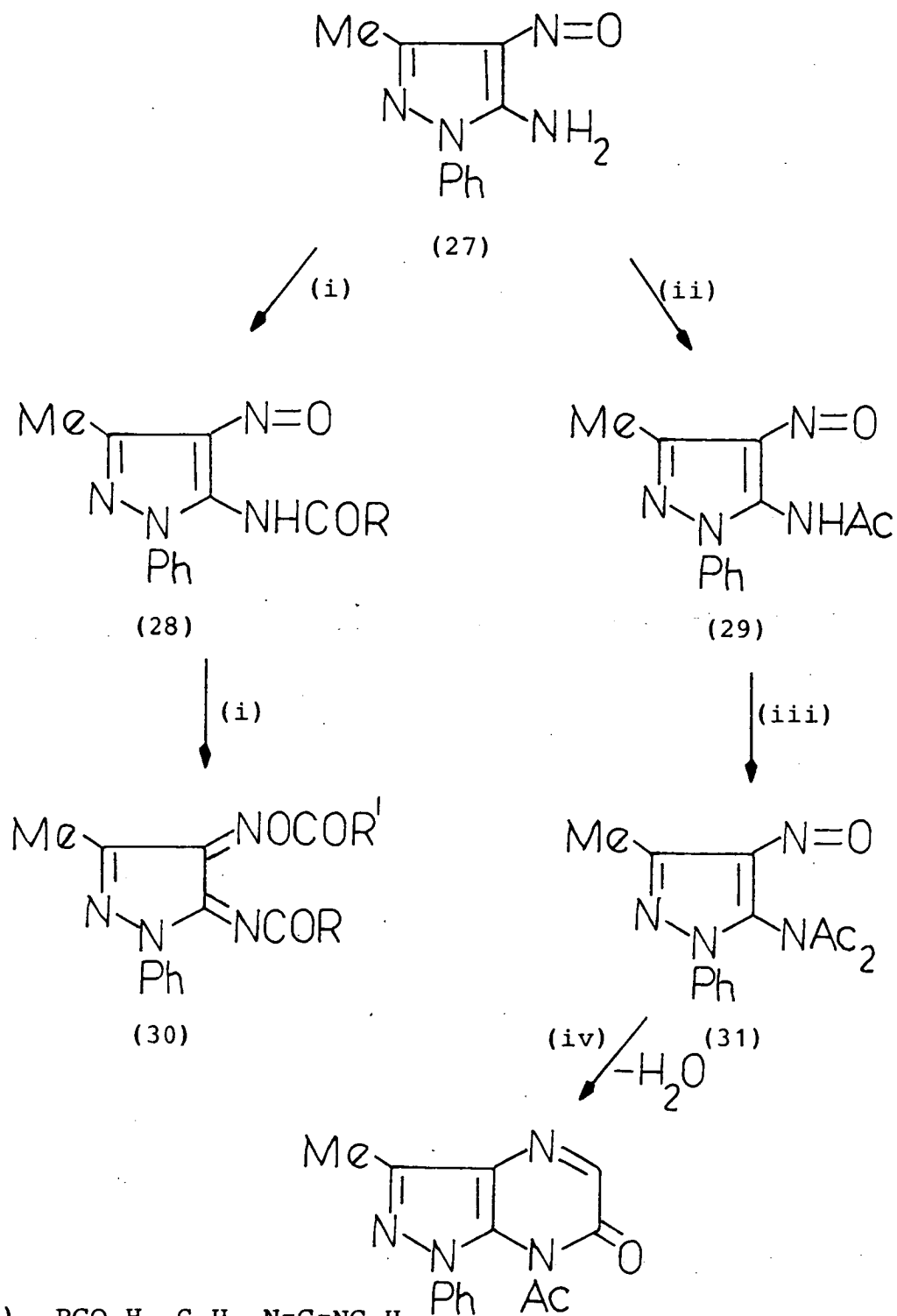
(i) base.

Scheme 5

with hydrogen peroxide was shown¹⁰⁴ to give the 4-N-oxide derivatives (14) in moderate yields and more recently¹⁰⁵ the synthesis of 1-phenylpyrazolo[3,4-b]pyrazine 4-N-oxide (15), as a potential anticancer agent was reported without experimental details. N-Oxygenated pyrazolo[3,4-b]pyrazines and their aza-analogues are of interest because of their potentially useful biological activity. The apparent lack of practical general methods for the synthesis of such compounds prompted the following investigations in this area.

(i) Investigations of New Synthetic Approaches to N-Oxygenated Pyrazolo[3,4-b]pyrazines

As already discussed at length in Chapters 1 and 2, the base-catalysed cyclisation of ortho-substituted nitrobenzene derivatives forms the basis of practical general routes to a variety of benz-fused N-oxygenated heterocycles.⁴³ However, the application (Scheme 4) of the base-catalysed cyclisation of ortho-substituted nitropyrazole derivatives to the synthesis of the required N-oxygenated pyrazolo[3,4-b]pyrazines [e.g. (16)+(17)+(18)+(19)] was considered impractical because of the relative inaccessibility of suitably functionalised aminonitropyrazoles such as (16). On the other hand, ortho-aminonitrosopyrazoles are readily accessible starting-materials.^{106,107} Therefore the approach to N-oxygenated pyrazolo[3,4-b]pyrazines (Scheme 5) adopted was based on the acylation of ortho-aminonitrosopyrazoles (20) with α -functionalised carboxylic acids (21; Y=OH) or carboxylic acid chlorides (21; Y=Cl) to afford the corresponding ortho-acetamido-nitrosopyrazoles (22). In the latter when the α -substituent (X) is electron-



(i) RCO_2H , $C_6H_{11}N=C=NC_6H_{11}$.

(ii) Ac_2O , room temperature.

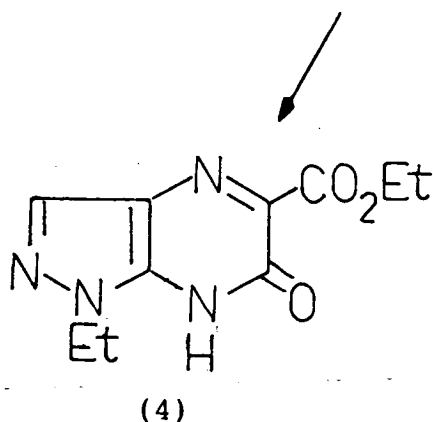
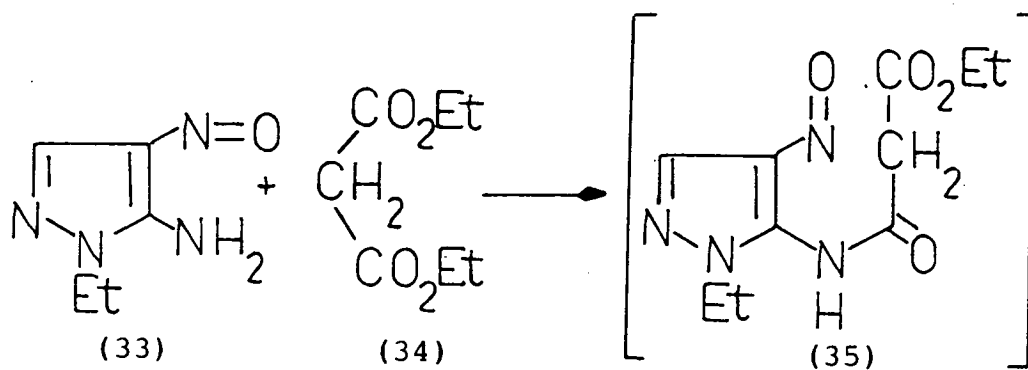
(iii) Ac_2O , 70° .

(iv) Ac_2O , heat, 1h.

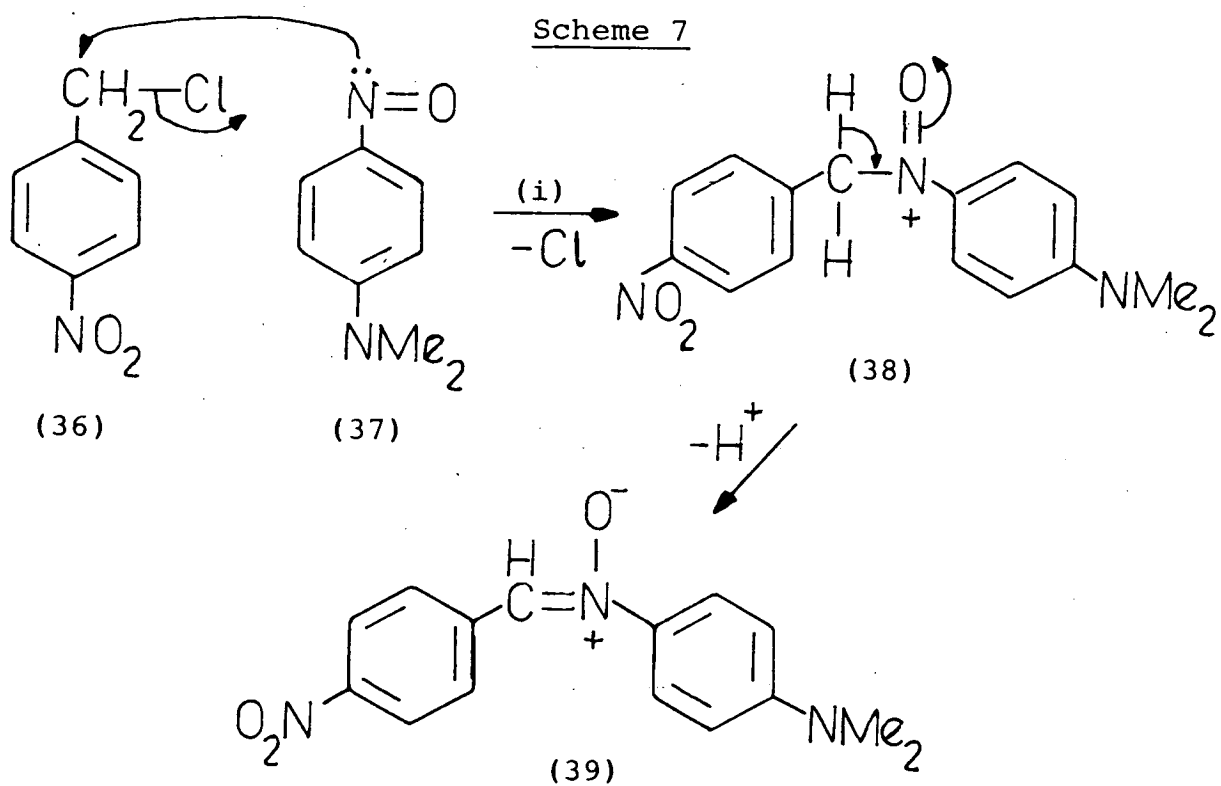
Scheme 6

withdrawing, but not a good leaving-group (e.g. acyl), base-catalysed cyclisation (Scheme 5) could be expected to afford cyclic hydroxylamines (23), which are prone to oxidation to the corresponding pyrazolo[3,4-b]pyrazinone N-oxides (25), while retaining the original α -substituent (X). Conversely when the α -substituent (X) in the ortho-acetamido-nitrosopyrazole (22) is both electron-withdrawing and a good leaving-group (e.g. cyano) base-catalysed cyclisation could be followed by elimination (Scheme 5) to afford pyrazolo[3,4-b]pyrazinone N-oxides (26) lacking the original α -substituent (X).

The formation of acetamido-nitrosopyrazoles [Scheme 5; (22)] has been reported in the literature by Guarneri and co-workers^{107,108} and is exemplified (Scheme 6) by the reaction of 5-amino-3-methyl-4-nitroso-1-phenylpyrazole (27) with acids in the presence of the condensation catalyst dicyclohexylcarbodiimide (DCC), to give the acetamidopyrazole derivative (28).¹⁰⁷ In these studies it was observed that further reaction with acid in the presence of DCC afforded the acyloxime-acyliminopyrazoles (30).¹⁰⁷ Further, it was demonstrated (Scheme 6)¹⁰⁸ that reaction of the amino-nitrosopyrazole (27) with aliphatic acid anhydrides such as acetic anhydride gave acylamino-nitrosopyrazoles [e.g. (29)] and diacylamino-nitrosopyrazoles [e.g. (31)] depending on the reaction conditions employed. These workers¹⁰⁸ also reported that further heating of the diacylamino-nitrosopyrazole (31) with acid anhydride resulted in thermal dehydration to the pyrazolo[3,4-b]pyrazinone (32). Hoehn⁹⁹ has reported the

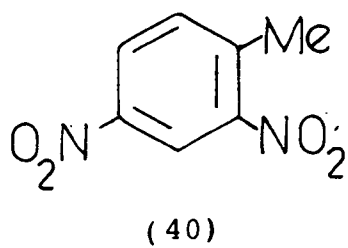


Scheme 7

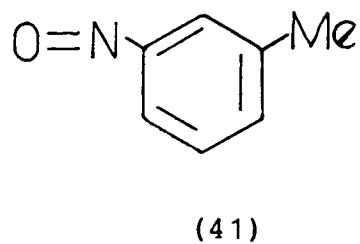


(i) MeOH, KOH.

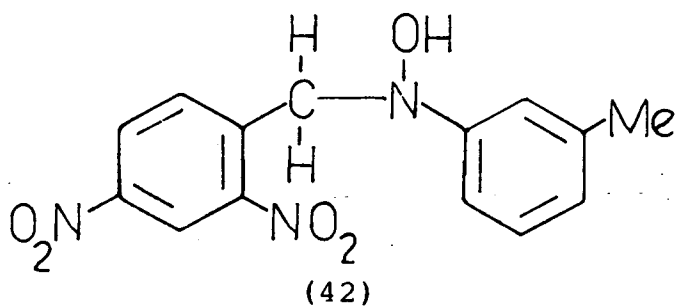
Scheme 8



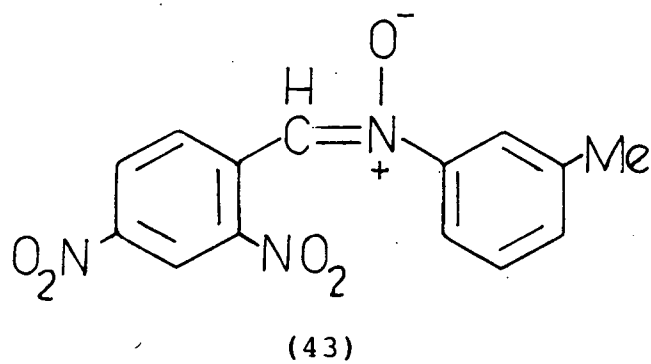
+



(i)



[O]

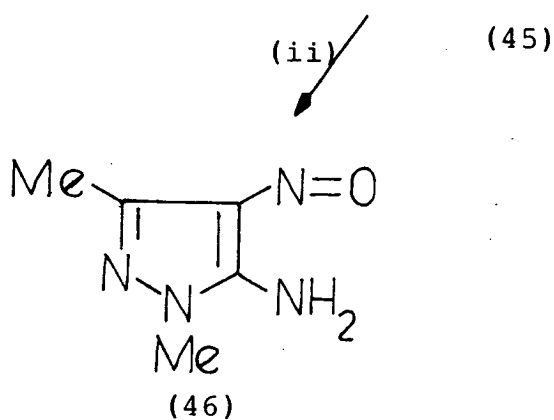
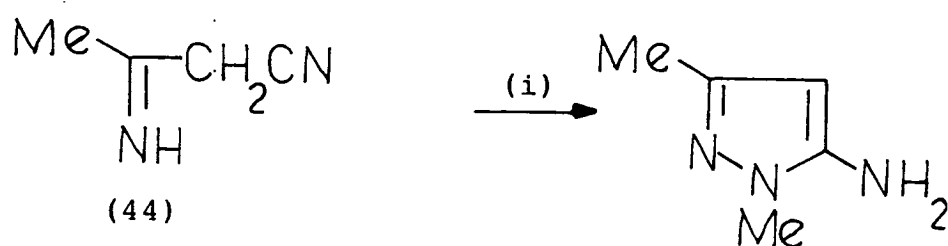


(i) Na_2CO_3 , piperidine.

Scheme 9

synthesis (Scheme 7) of pyrazolo[3,4-b]pyrazines [e.g. (4)] from the condensation of amino-nitrosopyrazoles (33) with diethyl malonate (34). This reaction presumably proceeds, by the intermediate formation and cyclisation of the acetamido-nitrosopyrazole (35). However neither Guarneri et al nor Hoehn have reported the synthesis of N-oxygenated pyrazolo[3,4-b]pyrazine derivatives.

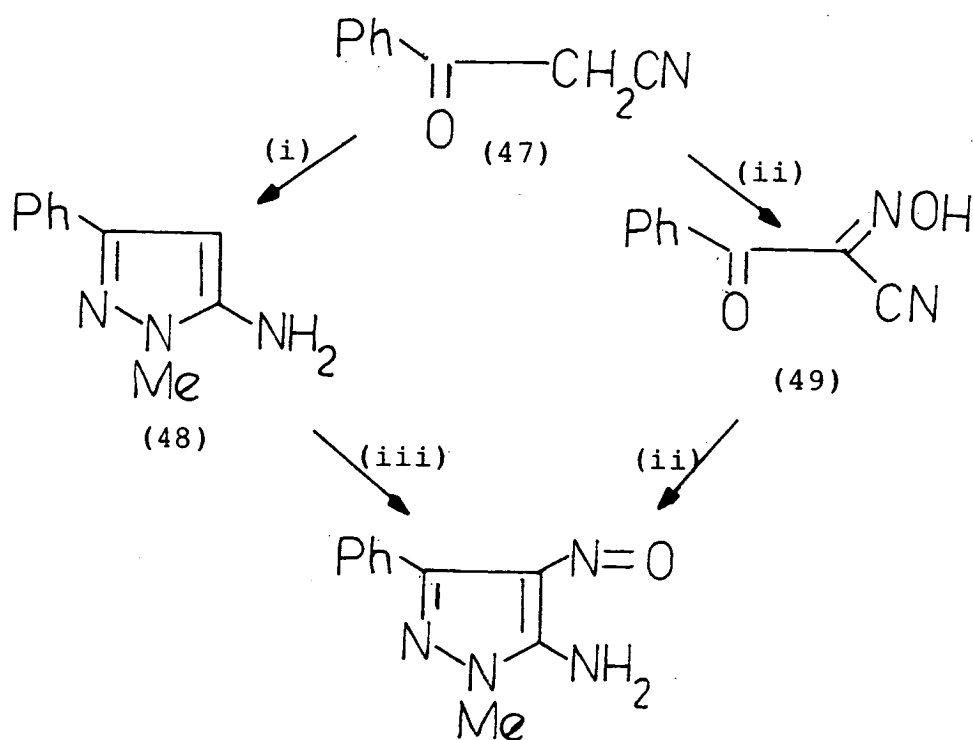
The proposed synthetic route (Scheme 5) to the desired N-oxygenated pyrazolo[3,4-b]pyrazines requires the ortho-acetamido-nitrosopyrazoles (22) to undergo intramolecular cyclisation through either the elimination of a suitably activated substituent X, with formation of the pyrazolo-pyrazinone N-oxides [(22)→(24)→(26)], or via an oxidative process by way of the hydroxylamine intermediates (23) to give the pyrazolopyrazinone N-oxides [(22)→(23)→(25)]. The formation of the pyrazolopyrazinone N-oxides (26) can be considered as an intramolecular version of the base-catalysed condensation (Scheme 8)¹⁰⁹ of para-nitrobenzyl chloride (36) with para-nitroso-N,N-dimethylaniline (37) to give the nitron (39). Similarly, formation (Scheme 5) of the pyrazolopyrazinone N-oxide (25) by oxidation of the hydroxylamine intermediate (23) might also be predicted by analogy with reactions reported in the literature. Tananescu and Nanu¹¹ reported (Scheme 9) the formation of the nitron (43) as the product of the reaction between 2,4-dinitrotoluene (40) and meta-nitrosotoluene (41) in piperidine in the presence of sodium carbonate. The product (43) is most readily explained in terms of the intermediate formation and in situ oxidation of the hydroxylamine intermediate (42).



(i) MeNHNH_2 , EtOH, heat.

(ii) NaNO_2 , AcOH, H_2O , $<12^\circ$.

Scheme 10



(i) MeNHNH_2 , EtOH, heat. (50)

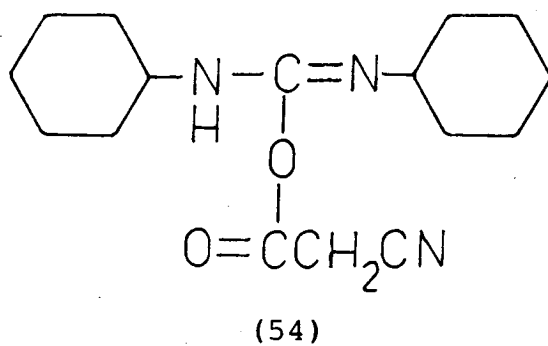
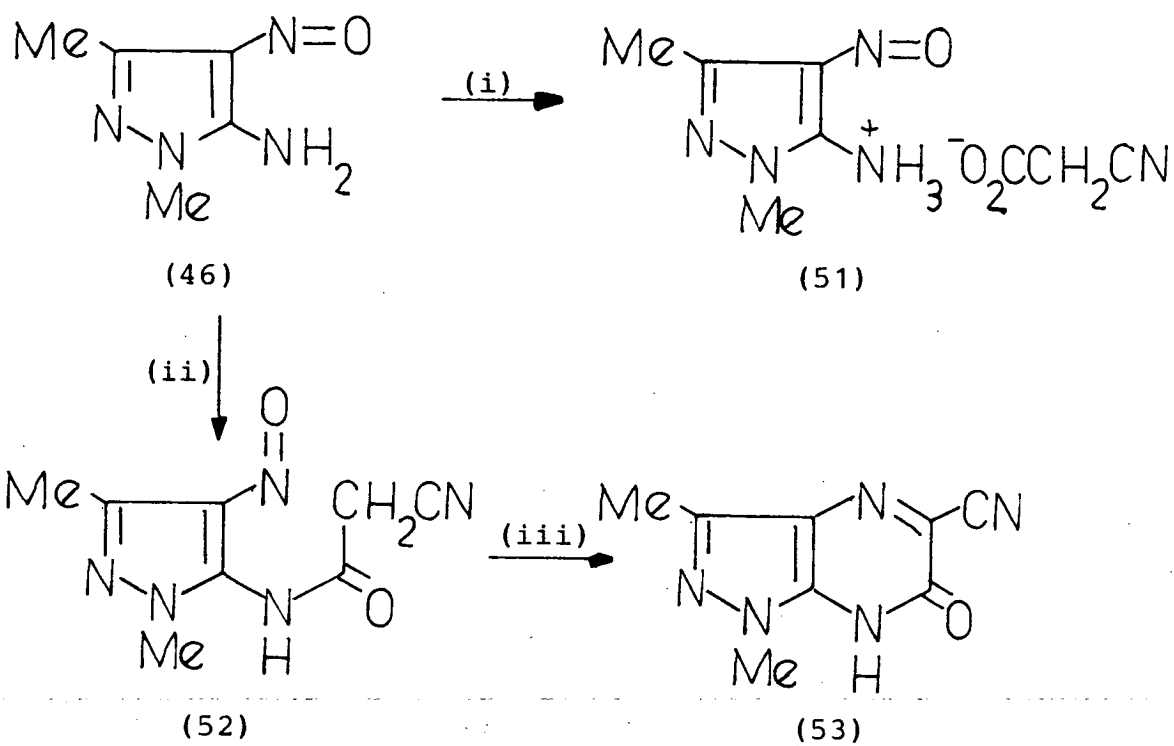
(ii) NaNO_2 , AcOH.

(iii) NaNO_2 , AcOH, H_2O , $<15^\circ$.

Scheme 11

ortho-Amino-nitrosopyrazoles required as starting-materials for the proposed N-oxygenated pyrazolo[3,4-b]-pyrazine syntheses (Scheme 5) were readily prepared by methods reported in the literature (Schemes 10 and 11). Thus 5-amino-1,3-dimethyl-4-nitrosopyrazole (46) was obtained¹⁰⁶ in good yield by the reaction (Scheme 10) of the commercially available β -iminocrotononitrile (44) with methylhydrazine to afford 5-amino-1,3-dimethylpyrazole (45), followed by C-nitrosation of the latter with sodium nitrite in aqueous acetic acid. Benzoylacetoneitrile (47), readily prepared¹¹¹ by the reaction of α -bromoacetophenone with aqueous ethanolic potassium cyanide, reacted (Scheme 11) with methylhydrazine to afford the known^{112,113} 5-amino-1-methyl-3-phenylpyrazole (48), nitrosation of which with sodium nitrite in aqueous acetic acid gave the required 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50)¹¹³ in high yield (97%). The amino-nitrosopyrazole (50) was also synthesised (Scheme 11) in somewhat lower yield (45%) by the reaction of the known¹¹⁴ oximinobenzoylacetoneitrile (49) with methyl hydrazine.

It was noted that the amino-nitrosopyrazoles (46) and (50) prepared as shown in Schemes 10 and 11 did not have the green colour associated with most nitroso compounds, suggesting that in the solid state they in fact exist (Scheme 5) predominantly in the tautomeric oxime form (20A). Also it was observed that solutions of the amino nitrosopyrazoles (46) and (50) in nonpolar solvents such as methylene chloride and 1,2-dimethoxyethane were green indicating that the nitroso form (20B) was predominant. However their solutions in ethanol and dioxane retained the red colour observed in the



(i) $\text{NCCH}_2\text{CO}_2\text{H}$, CH_2Cl_2 .

(ii) $\text{NCCH}_2\text{CO}_2\text{H}$, $\text{C}_6\text{H}_{11}\text{N}=\text{C}=\text{NC}_6\text{H}_{11}$, CH_2Cl_2 .

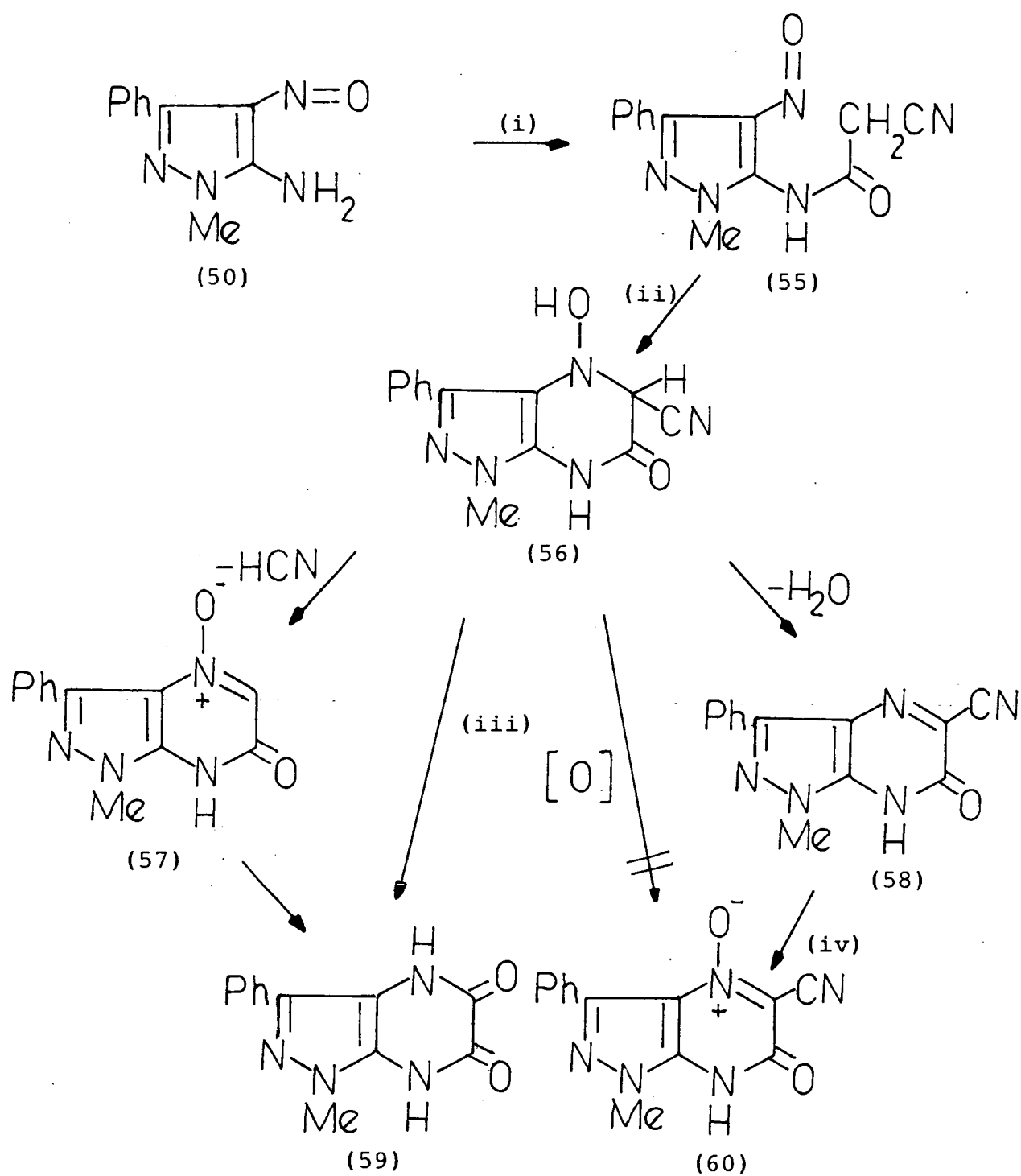
(iii) NaOH , H_2O .

Scheme 12

solid state, suggesting that in these solvents the tautomeric oxime form (20A) is dominant.

The general synthetic approaches to N-oxygenated pyrazolo[3,4-b]pyrazines outlined in Scheme 5 were first investigated (Scheme 12) using 5-amino-1,3-dimethyl-4-nitrosopyrazole (46). The intention was to convert this compound into the cyanoacetamido-derivative (52) in the expectation that this product would undergo base-catalysed cyclisation to afford either or both of the pyrazolo[3,4-b]pyrazinone N-oxides [Scheme 5; (25; R=Me, X=CN)] and [Scheme 5; (26; R=Me)]. Initially it was found that the uncatalysed reaction of the amino-nitrosopyrazole (46) with cyanoacetic acid in methylene chloride afforded an insoluble solid whose spectroscopic properties showed it to be the cyanoacetic acid salt (51). The identity of this compound was confirmed by its reconversion in aqueous sodium hydroxide into the amino-nitrosopyrazole (46) in moderate yield. To promote the desired condensation of the amino-nitrosopyrazole (46) with cyanoacetic acid to afford the amide (52) the reaction was carried out in the presence of the condensation catalyst dicyclohexylcarbodiimide (DCC). In practice, to avoid the unwanted formation of the salt (51), the amino-nitrosopyrazole (46) was added to a preformed solution of cyanoacetic acid and DCC in methylene chloride. Treatment of the resulting green suspension with aqueous sodium hydroxide gave a readily separated mixture of dicyclohexylurea and an alkali soluble product obtained in low yield (26%) which gave accurate mass data consistent with the molecular formula $C_8H_7N_5O$. The i.r. spectrum of this product showed cyano-absorption at

2240 cm^{-1} and lactam NH and carbonyl absorption at 3480 and 1680 cm^{-1} respectively, consistent with its formulation as the pyrazolopyrazinone structure (53). The green colour of the mixture obtained from the reaction of the amino-nitrosopyrazole (46) with cyanoacetic acid in the presence of DCC was indicative¹⁰⁷ of the initial formation of the expected nitrosopyrazole derivative (52) which presumably underwent cyclisation to the pyrazolopyrazinone (53) in the course of the aqueous alkaline workup. This hypothesis was verified by the direct chromatographic separation, without alkaline workup, of the mixture from the reaction of the amino-nitrosopyrazole (46) with cyanoacetic acid in the presence of DCC. This gave, together with unreacted amino-nitrosopyrazole (46) and dicyclohexylurea, low yields of two other products with melting-points 142° and 75° respectively. The higher melting product formed apple green crystals and gave accurate mass data in accord with the molecular formula, $\text{C}_8\text{H}_9\text{N}_5\text{O}_2$. These properties and the presence of amino and carbonyl absorption in its i.r. spectrum due to a secondary amide group, allow the formulation of the green product as the cyanoacetamido-nitrosopyrazole (52). The lower melting product gave accurate mass data which corresponds to the molecular formula $\text{C}_{16}\text{H}_{25}\text{N}_3\text{O}_2$. This together with the presence of NH and cyano absorption at 3300 and 2260 and 2180 cm^{-1} as well as high frequency carbonyl absorption at 1715 cm^{-1} in its i.r. spectrum allow the tentative formulation of the low melting product as the isourea derivative (54). Since this compound is the reactive intermediate involved in the formation of the amide (52) from the amino-nitrosopyrazole (46) its isolation is indicative of the



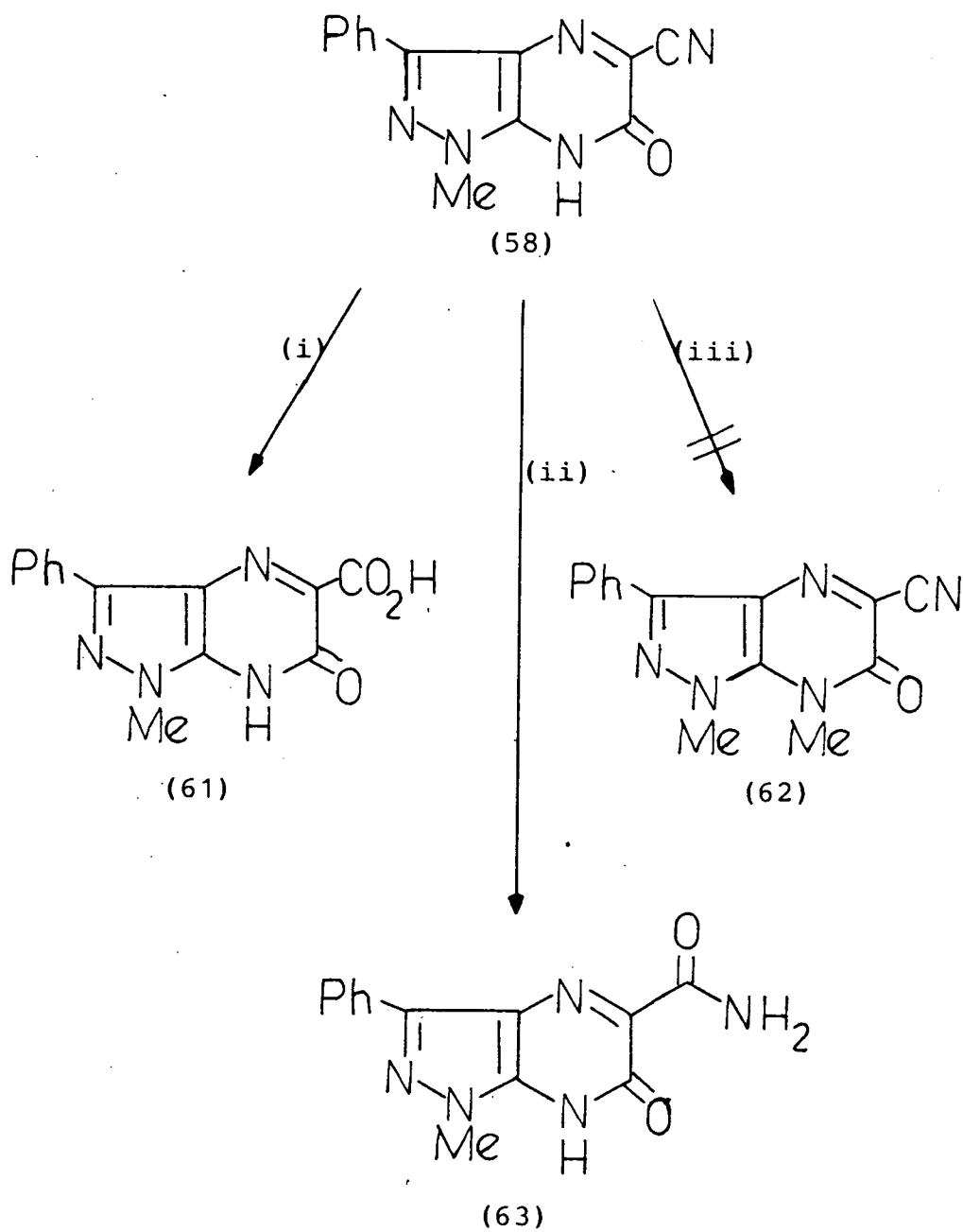
(i) $\text{NCCH}_2\text{CO}_2\text{H}$, $\text{C}_6\text{H}_{11}\text{N}=\text{C}=\text{NC}_6\text{H}_{11}$.

(ii) NaOH , H_2O .

(iii) MnO_2 , H_2O , NaOH (aq).

(iv) H_2O_2 , H_2O , 50° .

Scheme 13



- (i) 20% w/v KOH-H₂O, heat.
- (ii) H₃PO₄-P₂O₅, heat.
- (iii) NaH, MeI, Me₂NCH=O or 10% w/v NaOH-H₂O, Me₂SO₄.

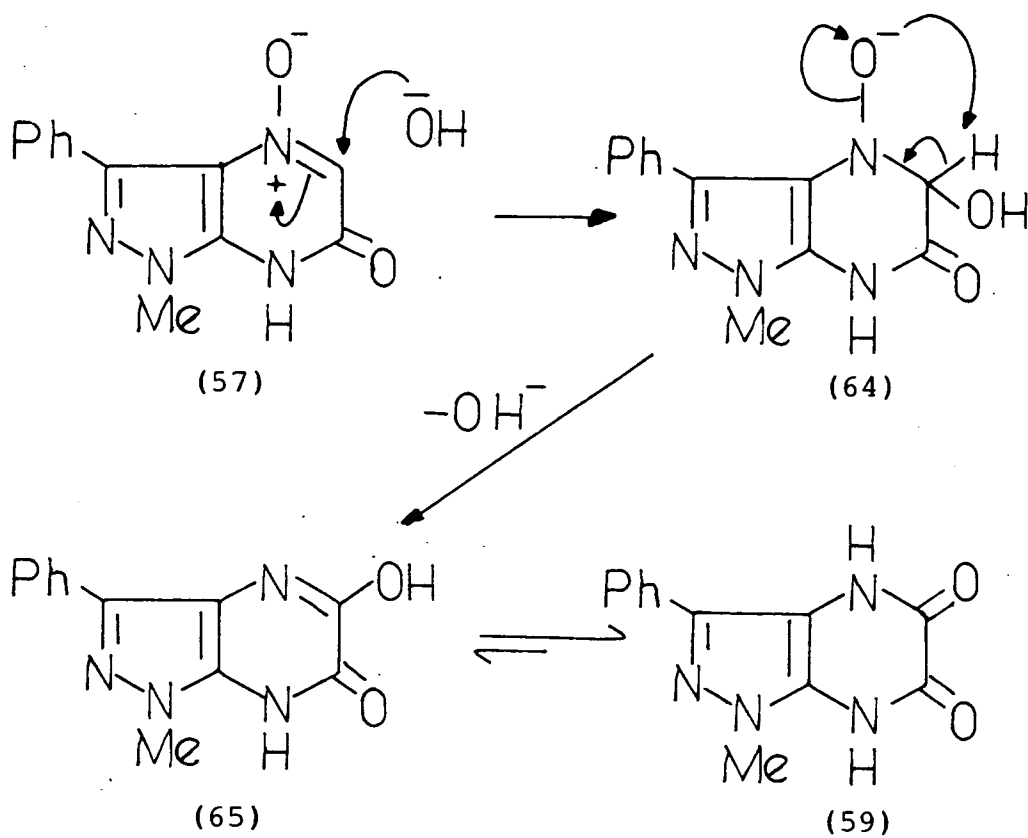
Scheme 14

low reactivity of the amino-group in the latter material.

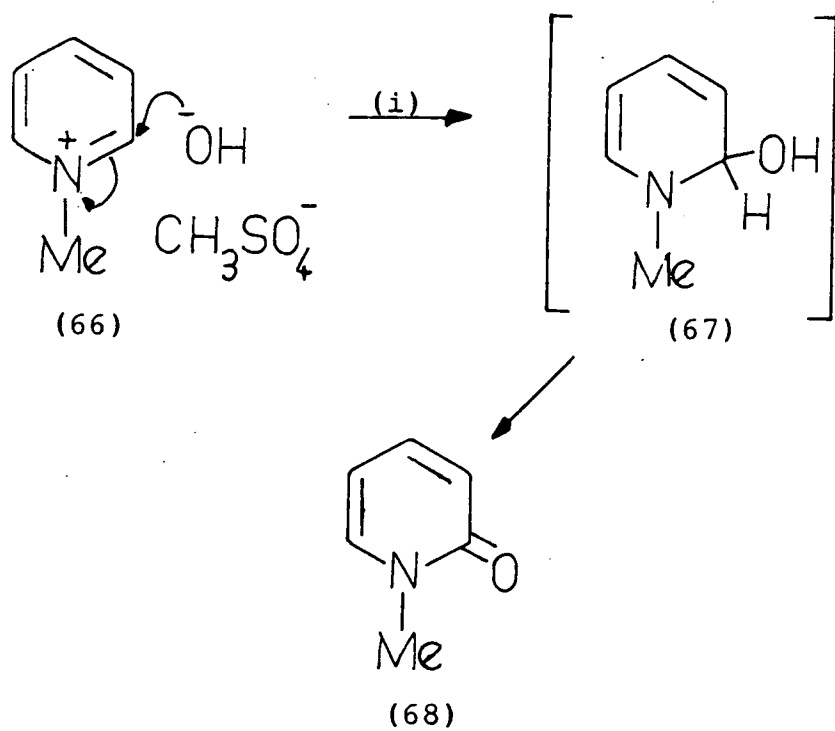
The formation of the cyanoacetamido-nitrosopyrazole (52) in only very low yield from the reaction of the amino-nitrosopyrazole (46) with cyanoacetic acid in the presence of DCC precluded the study of its base-catalysed cyclisation to the pyrazolopyrazinone N-oxides [Scheme 5, (25; R=Me, X=CN)] and [Scheme 5, (26; R=Me)]. In consequence attention was turned (Scheme 13) to the study of the reaction of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) with cyanoacetic acid in the hope of obtaining the cyanoacetamido-nitrosopyrazole (55) and by cyclisation of the latter, the pyrazolopyrazinone N-oxides (57) and (60). In practice the amino-nitrosopyrazole (50) reacted with cyanoacetic acid in methylene chloride in the presence of DCC to give a green product mixture which was separated by treatment with aqueous sodium hydroxide into dicyclohexylurea and a high yield of a yellow alkali soluble product, which gave accurate mass data consistent with the pyrazolopyrazinone structure (58). This formulation was further supported by the product's spectroscopic properties. In particular its i.r. spectrum contained cyano-absorption at 2230 cm^{-1} and bands at 3100 to 2700 and 1655 cm^{-1} attributable to the NH and carbonyl components of the cyclic amide structure (58). This structure for the yellow acidic product was firmly established (Scheme 14) by its hydrolysis in 20% w/v aqueous potassium hydroxide solution to afford the corresponding carboxylic acid (61) in high yield (93%). Conversely, heating the cyanopyrazolopyrazinone (58) in polyphosphoric acid afforded a good yield of the carboxamide (63). The analytical and spectroscopic properties of the carboxylic

acid (61) and the carboxamide (63) were fully in accord with the assigned structures. However, the attempted conversion of the cyanopyrazolopyrazinone (58) into the N-methyl derivative (62) by methylation with sodium hydride-methyl iodide or aqueous sodium hydroxide-dimethyl sulphate gave only a high recovery (>80%) of the unreacted starting material (58).

The green colour of the mixture obtained from the reaction of the amino-nitrosopyrazole (50) with cyanoacetic acid in the presence of DCC suggested the initial formation of the cyanoacetamido-nitrosopyrazole (55). Under the alkaline conditions of workup, needed to isolate product free of dicyclohexylurea, this presumably cyclised to the cyanopyrazolopyrazinone (58), thus accounting for the formation of this product. The isolation of the cyanopyrazolopyrazinone (58) is also indicative of the intermediate formation of the cyclic hydroxylamine (56), which undergoes dehydration to give (58) rather than elimination to afford the originally hoped for pyrazolopyrazinone N-oxide (60). Several attempts were made to achieve the in situ oxidation of the presumed cyclic hydroxylamine intermediate (56) to the required pyrazolopyrazinone N-oxide (60). The green mixture, presumed to contain the nitroso-pyrazole derivative (55), obtained as above, was treated with manganese dioxide in aqueous alkaline solution. This afforded a good yield of an acidic product which gave analytical data in accord with the molecular formula $C_{12}H_{10}N_4O_2$. The i.r. spectrum of this product lacked cyano-absorption, but contained NH and carbonyl absorption at 3300 to 2500 and 1695 cm^{-1} , typical of a cyclic



Scheme 15



(i) $\text{K}_3\text{Fe}(\text{CN})_6$, NaOH , H_2O .

Scheme 16

amide structure. On the basis of its spectral properties and the observed analytical data, the acidic compound is tentatively assigned the pyrazolopyrazinedione structure (59). The formation of this product is interesting and can be explained (Scheme 15) by an initial base-catalysed cyclisation of the cyanoacetamido-nitrosopyrazole (55) to the pyrazolo-[3,4-b]pyrazine N-oxide (57). Hydration then dehydration under the aqueous alkaline conditions would then afford the 5-hydroxy-1-methyl-3-phenylpyrazolo[3,4-b]pyrazin-6-one (65), tautomerisation of which accounts for the formation of the observed product (59).

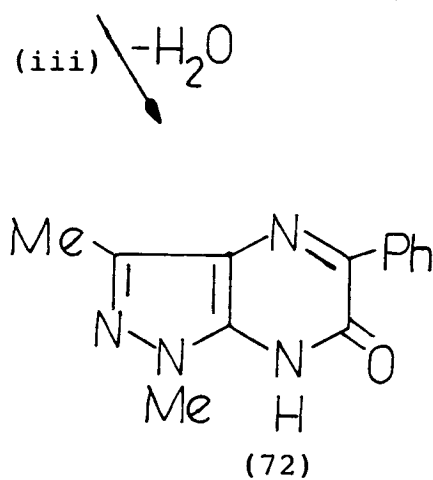
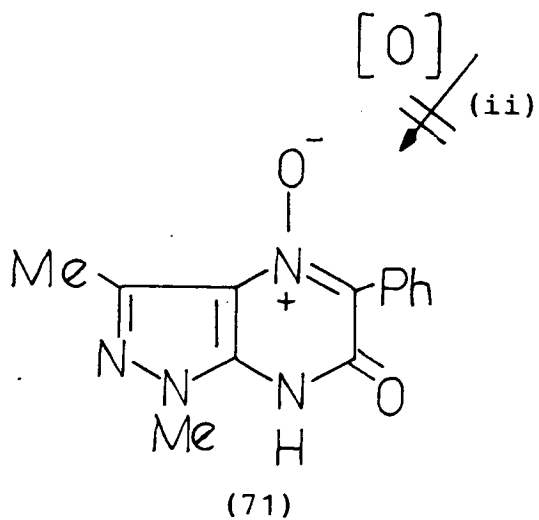
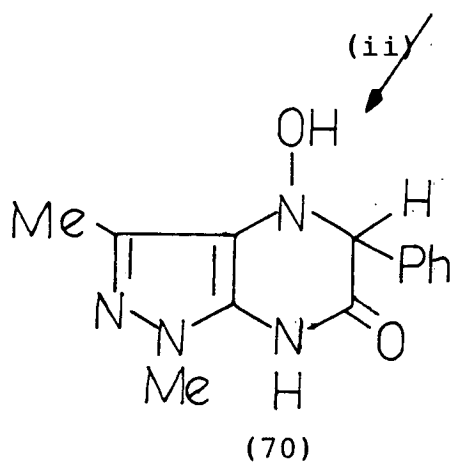
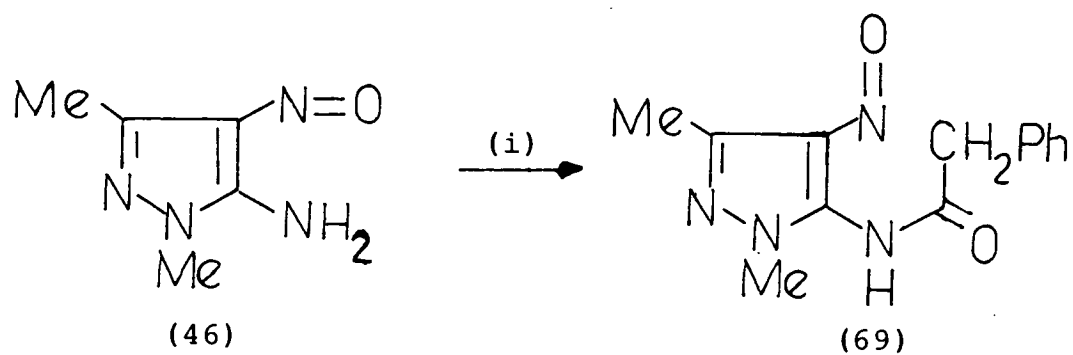
In an attempt to induce the oxidative base-catalysed cyclisation to the 5-cyanopyrazolopyrazinone N-oxide (60), it was decided to investigate an alternative oxidising agent to manganese dioxide, which would not require the use of a strongly alkaline medium. Aqueous sodium hypochlorite was chosen as the oxidant on the assumption that its mildly basic character would promote the initial base-catalysed cyclisation without the need for added alkali. Thus treatment of the amino-nitrosopyrazole (50) with cyanoacetic acid in the presence of DCC as before gave the usual green solid containing the cyanoacetamido-nitrosopyrazole (55). However treatment of this with aqueous sodium hypochlorate afforded only a good yield of dicyclohexylurea and an intractable brown solid from which no identifiable material could be obtained.

In a further attempt to achieve the base-catalysed oxidative cyclisation of the cyanoacetamido-nitrosopyrazole (55) to the N-oxygenated pyrazolopyrazinone (60), it was next decided to investigate the use of potassium ferricyanide in

aqueous alkaline solution as the oxidising medium. Potassium ferricyanide in aqueous sodium hydroxide has been used (Scheme 16)¹¹⁵ to oxidise heterocyclic pseudo-bases [e.g. (67)] to the corresponding lactams [e.g. (68)]. However treatment of the green solid containing the cyanoacetamido-nitrosopyrazole (55) with potassium ferricyanide in aqueous alkaline solution only afforded good yields of dicyclohexylurea and an alkali soluble product, which was shown to be impure 5-cyano-1-methyl-3-phenylpyrazolo[3,4-b]pyrazin-6(7H)-one (58) by comparison with an authentic sample prepared previously. None of the desired N-oxygenated pyrazolo[3,4-b]pyrazinone (60) was observed.

Having failed to achieve the synthesis of the 5-cyano-pyrazolopyrazinone N-oxide (60) directly from the cyclisation of the cyanoacetamido-nitrosopyrazole (55) an attempt was made to oxidise the 5-cyano-1-methyl-3-phenylpyrazolo[3,4-b]pyrazin-6(7H)-one (58) to the desired N-oxygenated derivative (60). Korbukh et al.¹⁰⁴ reported (Scheme 3) the peroxide oxidation of the pyrazolopyrazines (13) to the 4-N-oxides (14) in low yield. However, treatment of the pyrazolopyrazinone (58) with aqueous hydrogen peroxide failed to give an N-oxygenated product, the unreacted starting material (58) being recovered in good yield.

The synthesis of N-oxygenated pyrazolo[3,4-b]pyrazinones [Scheme 5, (25) and/or (26)] from the cyanoacetamido-nitrosopyrazoles (52) and (55) was complicated by difficulties in isolating the latter in pure form because of the necessity for an aqueous alkaline workup in their preparation to remove dicyclohexylurea from the reaction mixtures. The methylene protons of the cyanoacetamido-nitrosopyrazoles (52) and (55)



(i) $C_6H_5CH_2CO_2H$, $C_6H_{11}N=C=NC_6H_{11}$, CH_2Cl_2 .

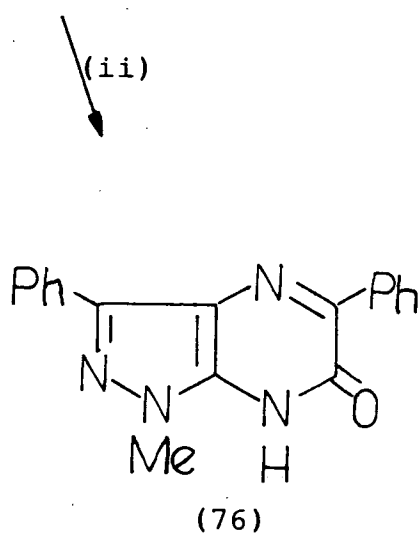
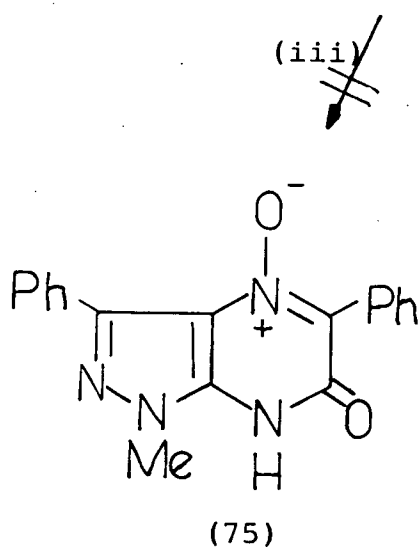
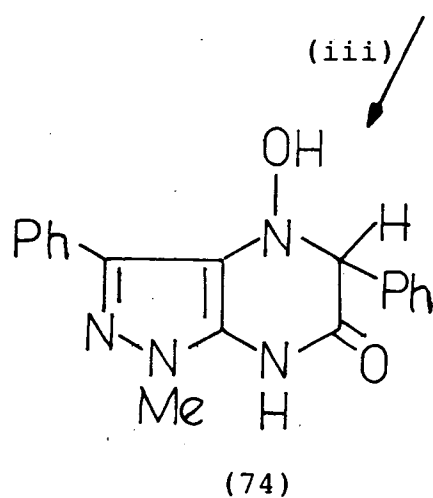
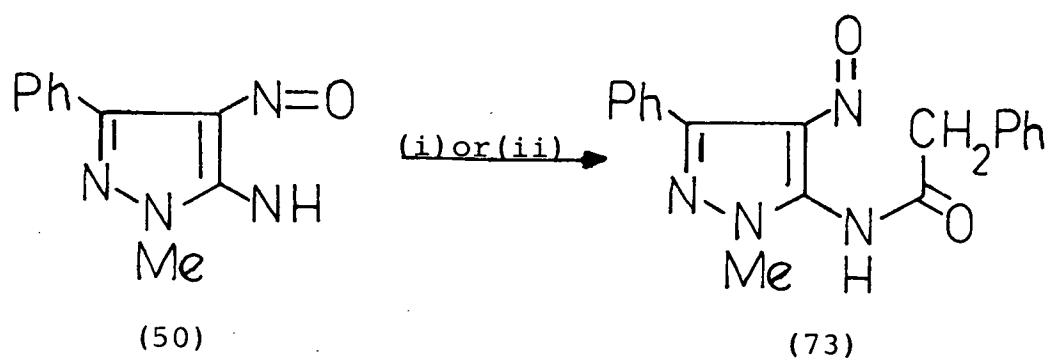
(ii) base.

(iii) NaOEt, EtOH, heat.

Scheme 17

are activated by the α -cyano substituent and on treatment with base these compounds readily undergo dehydrative cyclisation involving the nitroso substituent to give the observed 5-cyanopyrazolo[3,4-b]pyrazinones (53) and (56). Therefore, attempts were made to synthesise alternative α -substituted acetamido-nitrosopyrazoles in which the methylene protons were less acidic. It was considered that such acetamido-nitrosopyrazoles would not be so prone to undergo base-catalysed cyclisation, and thus could be readily separated from dicyclohexylurea on aqueous alkaline workup.

In practice (Scheme 17) treatment of 5-amino-1,3-dimethyl-4-nitrosopyrazole (46) with phenylacetic acid in the presence of DCC, followed by treatment with aqueous alkali to separate the product from dicyclohexylurea, afforded a green solid which gave accurate mass data consistent with the molecular formula $C_{13}H_{14}N_4O_2$. This, together with the observed spectroscopic properties of the product allowed its formulation as the 1,3-dimethyl-4-nitroso-5-phenylacetamidopyrazole (69). In particular the i.r. spectrum of this compound showed NH and carbonyl absorption at 3200 and 1690 cm^{-1} respectively, consistent with a secondary amide structure. Also the 1H n.m.r. spectrum exhibited a sharp singlet at 3.78 due to the protons of a methylene group together with the expected NH, aromatic and methyl proton resonances. Unfortunately, the attempted sodium ethoxide catalysed cyclisation of the phenylacetamidopyrazole (69) failed to give the desired pyrazolo-pyrazinone N-oxide (71). The observed product, formed in low yield, was a yellow crystalline solid which gave accurate mass data consistent with its formulation as 1,3-dimethyl-5-



- (i) $\text{PhCH}_2\text{CO}_2\text{H}$, $\text{C}_6\text{H}_{11}\text{N}=\text{C}=\text{NC}_6\text{H}_{11}$, CH_2Cl_2 .
 (ii) PhCH_2COCl , Et_3N , dioxane.
 (iii) base.

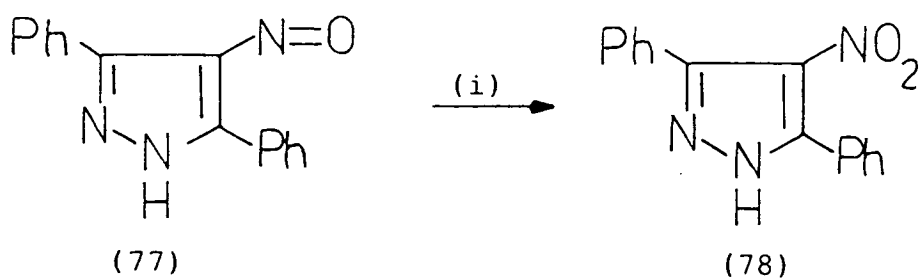
phenylpyrazolo[3,4-b]pyrazin-6(7H)-one (72). The i.r. spectrum of this product showed NH and carbonyl absorption at 3200-2550 and 1640 cm^{-1} respectively and was consistent with the proposed structure (72).

Having failed to effect the base-catalysed cyclisation of the nitroso-phenylacetamidopyrazole (69) to the N-oxygenated pyrazolopyrazinone (71), attention was turned to the synthesis (Scheme 18) of 1-methyl-4-nitroso-3-phenyl-5-phenylacetamidopyrazole (73) and its subsequent cyclisation to the pyrazolopyrazinone N-oxide (75). Treatment of the amino-nitrosopyrazole (50) with phenylacetic acid in the presence of DCC gave, on aqueous alkaline workup to separate the product from dicyclohexylurea, a low yield (26%) of a green crystalline solid whose analytical and mass spectral properties were consistent with the phenylacetamidopyrazole structure (73). The i.r. spectrum of the phenylacetamidopyrazole (73) showed the expected NH and carbonyl absorption at 3200 and 1710 cm^{-1} . The only curious feature of the compound's ^1H n.m.r. spectrum was overlapping of the signals due to the methyl and methylene protons at $\delta 3.76$, the NH and aromatic proton resonances being as expected. In an attempt to improve the yield of the nitroso-phenylacetamidopyrazole (73) its synthesis by the reaction of the amino-nitrosopyrazole (50) with phenylacetyl chloride in the presence of triethylamine was investigated. However this reaction gave a low recovery of the unreacted starting-material (50), together with low yields of two products with melting points 317-321° and 132-135° respectively. The lower melting product was green in colour and was identified as the nitroso-phenylacetamidopyrazole (73) by comparison with

the sample prepared previously. The higher melting product gave accurate mass data consistent with the molecular formula $C_{18}H_{14}N_4O$ and its i.r. spectrum showed NH and carbonyl absorption at 3120 to 2500 and 1645 cm^{-1} respectively. These properties allow the formulation of this product as 3,5-diphenyl-1-methylpyrazolo[3,4-b]pyrazin-6(7H)-one (76), which presumably arises by the triethylamine-catalysed cyclisation of the phenylacetamidopyrazole (73) to the cyclic hydroxylamine intermediate (74) followed by dehydration (Scheme 18). The low yields of the nitroso-phenylacetamidopyrazole (73) obtained in both of the synthetic routes investigated prevented the proposed study of its cyclisation to the pyrazolo[3,4-b]pyrazinone N-oxide (75),

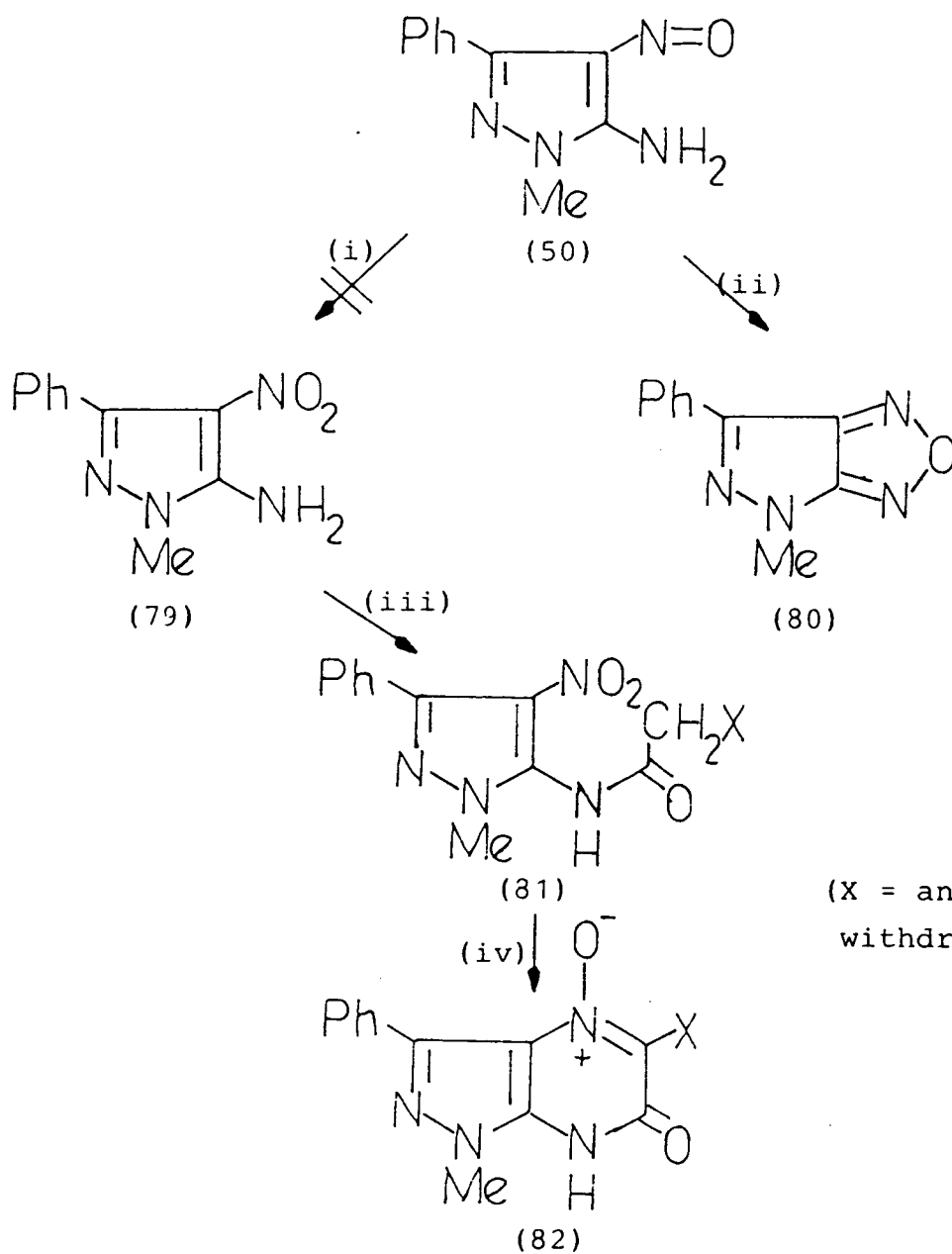
Due to the tendency of α -substituted acetamido-nitroso-pyrazoles to undergo cyclisation to pyrazolo[3,4-b]pyrazinone derivatives as opposed to the desired N-oxides (see Schemes 12, 13, 17 and 18) it was decided to adopt an alternative synthetic approach. This involved the synthesis (Scheme 4) of nitropyrazole derivatives (16) suitable for further elaboration to N-oxygenated pyrazolopyrazinones (19). Thus, reaction of the nitropyrazole derivatives (16) with suitable acid chlorides (17) could provide the α -substituted acetamido-nitropyrazoles (18) appropriately functionalised to undergo base-catalysed cyclisation to the desired pyrazolo[3,4-b]pyrazinone 4-N-oxides (19). Base-catalysed cyclisation of this type involving ortho-substituted nitrobenzene derivatives have been discussed at length in Chapters 1 and 2.

In general¹¹⁶ the synthesis of nitropyrazoles (16) may



(i) HNO_3 .

Scheme 19



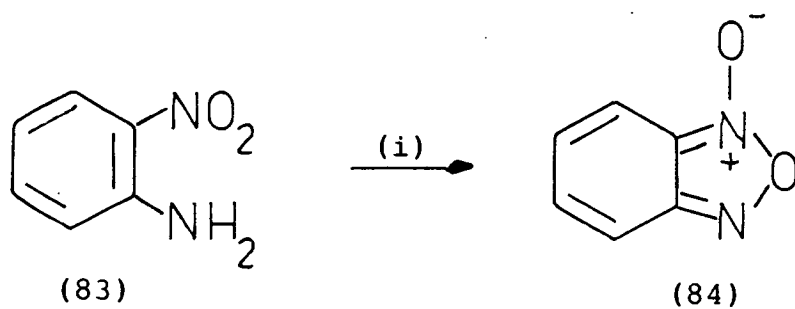
(i) MnO_2 , $\text{MeO}(\text{CH}_2)_2\text{OMe}$, room temp.

(ii) NaOCl , KOH , H_2O , 0° .

(iii) XCH_2COCl .

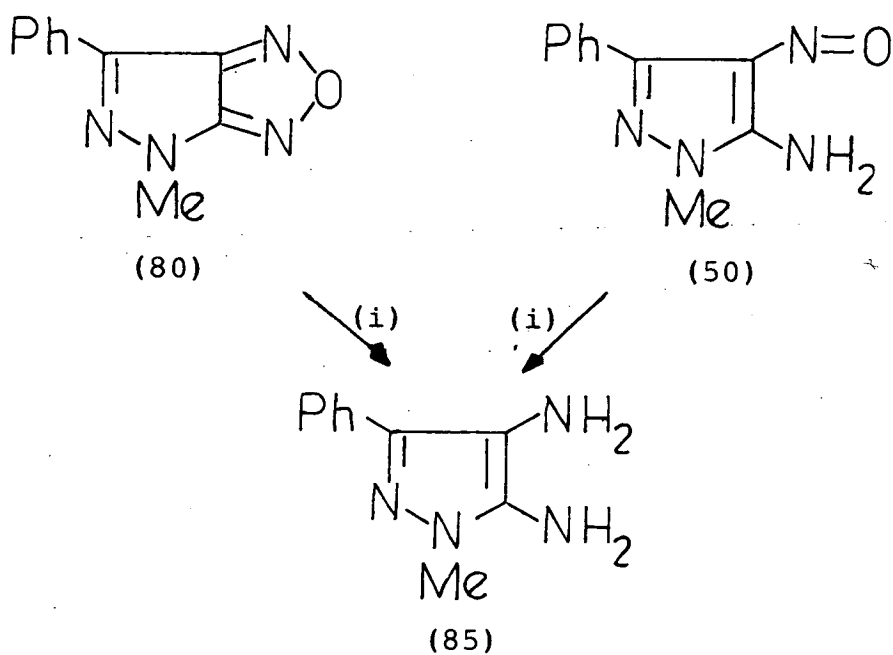
(iv) base.

Scheme 20



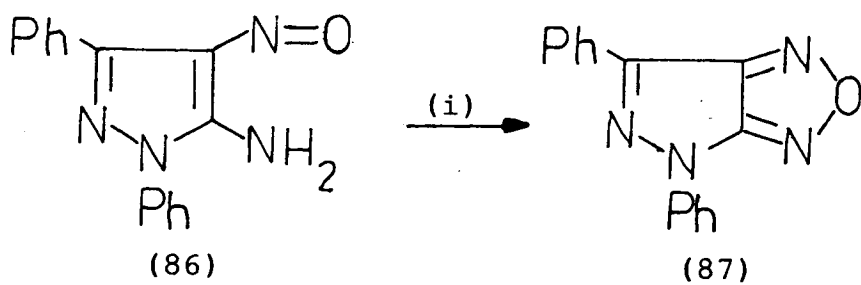
(i) NaOCl , NaOH , H_2O .

Scheme 21



(i) H_2 , Pd-C , EtOH .

Scheme 22

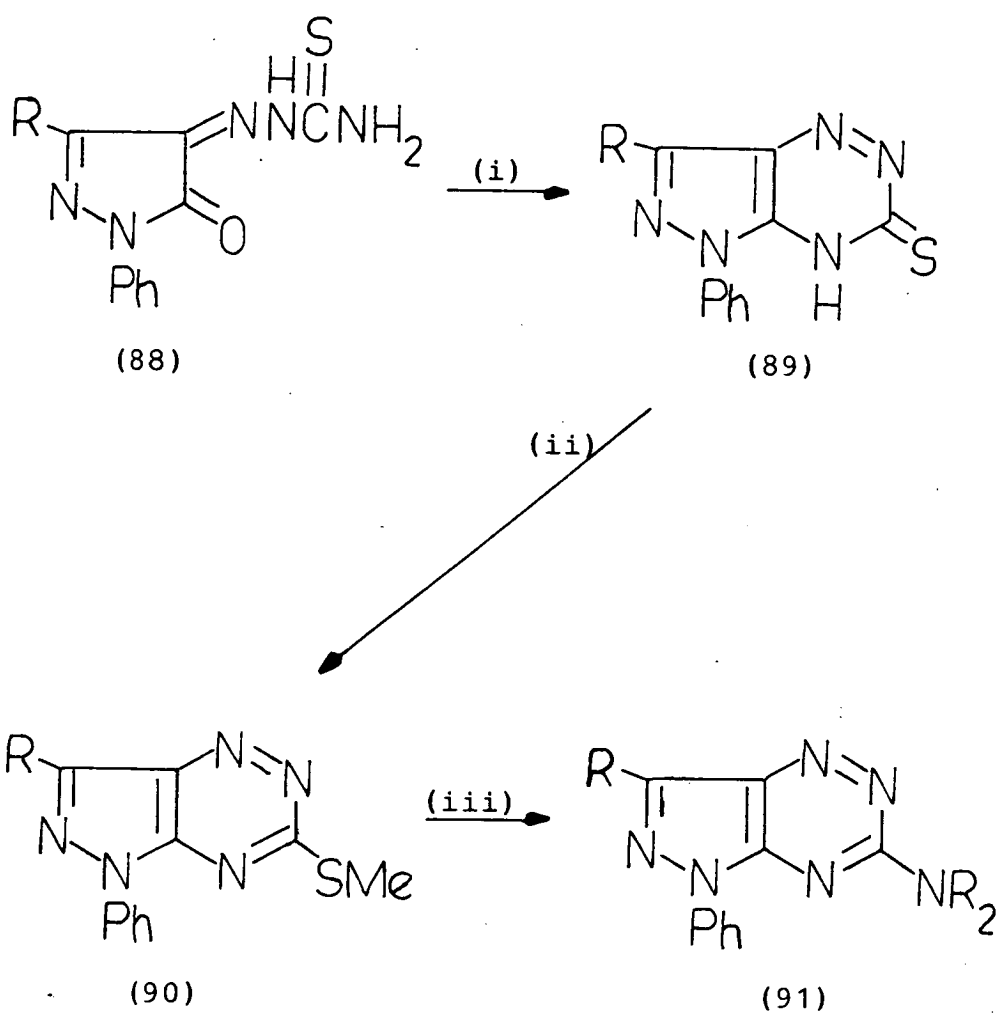


(i) KOCl , KOH , H_2O .

Scheme 23

be achieved by oxidation of the corresponding nitroso derivative as exemplified (Scheme 19) by the nitric acid oxidation¹¹⁷ of the diphenyl-nitrosopyrazole (77) to the corresponding nitropyrazole derivative (78) in moderate yield. The oxidation of nitroso compounds to the corresponding nitro derivatives can be carried out by a wide variety of oxidising agents¹¹⁸ and often under very mild conditions. The facility of nitroso to nitro oxidation accounts for the low yields usually obtained in attempts to synthesise nitroso compounds by oxidation of amines. Manganese dioxide is a mild though versatile oxidising agent and it was hoped might achieve the oxidation (Scheme 20) of the amino-nitrosopyrazole (50) to the amino-nitropyrazole (79) without affecting the amino-substituent. The intention was then to convert the latter compound into α -substituted acetamido-nitropyrazoles (81) and further by base-catalysed cyclisation into the corresponding pyrazolopyrazinone N-oxides (82). In practice (Scheme 20) the attempted oxidation of the amino-nitrosopyrazole (50) with manganese dioxide in 1,2-dimethoxyethane was unsuccessful, only a high recovery of the unreacted starting material (50) being obtained. This precluded the proposed study of the synthesis of N-oxygenated pyrazolopyrazinones (82) as detailed in Scheme 20 [(79)→(81)→(82)]. In view of the stability of the amino-nitrosopyrazole (50) to oxidation with manganese dioxide it was decided in passing to further examine the behaviour of this compound towards mild oxidation. Since sodium hypochlorite is known (Scheme 21) to oxidise ortho-aminonitrobenzenes (83) to benzofuroxans (84) it was of interest to study the effect of this oxidant on the amino-

nitrosopyrazole (50). The latter was found to react with sodium hypochlorite (Scheme 20) in the presence of aqueous potassium hydroxide to afford a high yield of a yellow solid, purified by vacuum sublimation, which gave accurate mass data consistent with the molecular formula $C_{10}H_8N_4O$. The i.r. spectrum of this material showed only C=N absorption at 1630 cm^{-1} and its ^1H n.m.r. spectrum contained only signals due to the protons of a phenyl and an N-methyl substituent. These features are consistent with the 1-methyl-3-phenyl-pyrazolo[3,4-d]furazan structure (80). In an attempt to obtain further evidence (Scheme 22) for the pyrazolofurazan structure (80) the product was hydrogenated over palladium-on-charcoal to give a solid, whose properties were consistent with its formulation as the 4,5-diaminopyrazole (85). This structure was confirmed by the preparation of an authentic sample by catalytic hydrogenation of the amino-nitrosopyrazole (50) which afforded a product which gave accurate mass data and showed spectroscopic properties in accord with the known¹⁰² 4,5-diaminopyrazole structure (85). The synthesis of pyrazolo[3,4-d]furazans by the oxidative cyclisation of 5-amino-4-nitrosopyrazoles has been described by Bertelson et al.¹¹⁹ as exemplified (Scheme 23) by the oxidative cyclisation of the amino-nitrosopyrazole (86) to the 1,3-diphenyl-pyrazolo[3,4-d]furazan (87) on treatment with potassium hypochlorite.

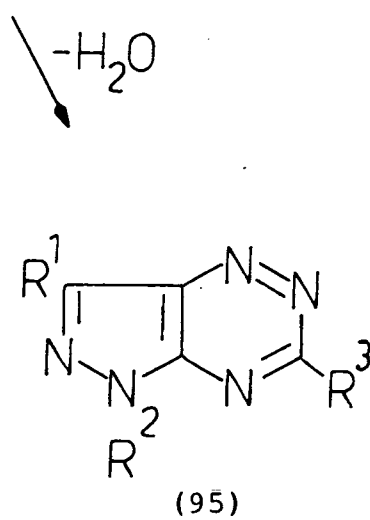
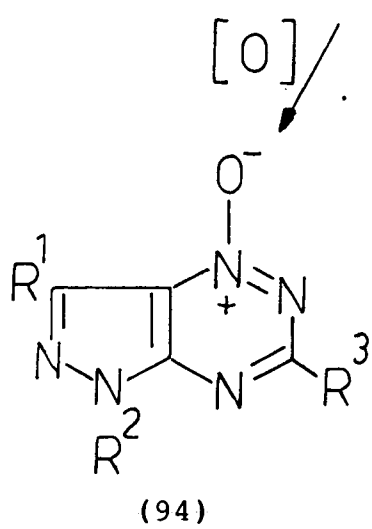
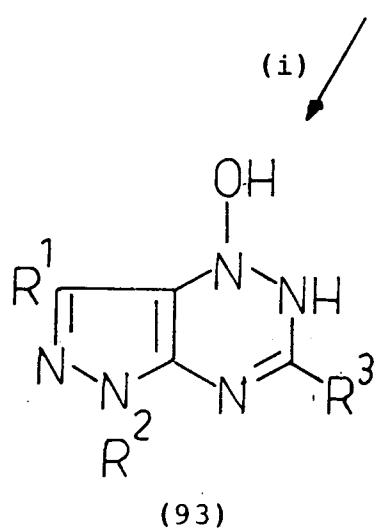
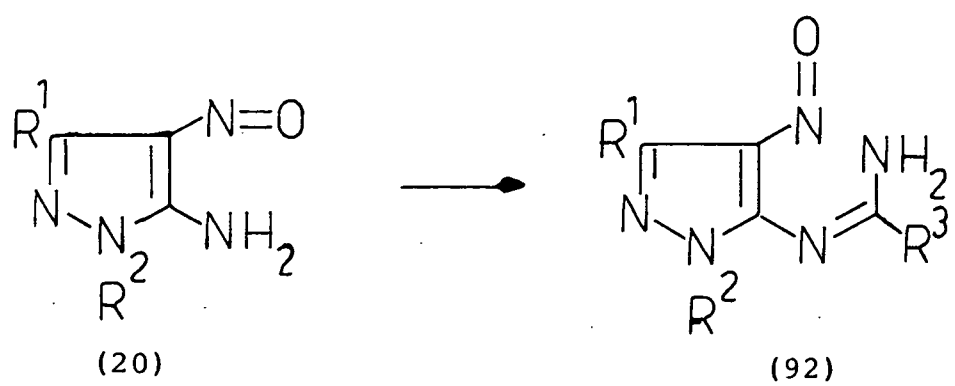


(i) K_2CO_3 , H_2O , heat.

(ii) NaOH , Me_2SO_4 .

(iii) R_2NH , heat.

Scheme 24



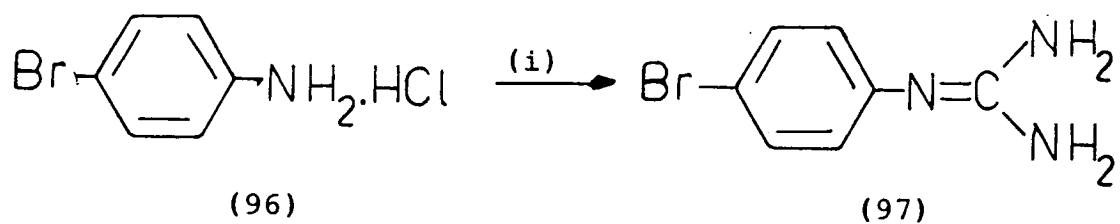
(i) base.

Scheme 25

(ii) Investigations of New Synthetic Approaches to N-Oxygenated Derivatives of Pyrazolo[3,4-e]-1,2,4-triazines and Related Polyaza-heterocyclic Ring Systems

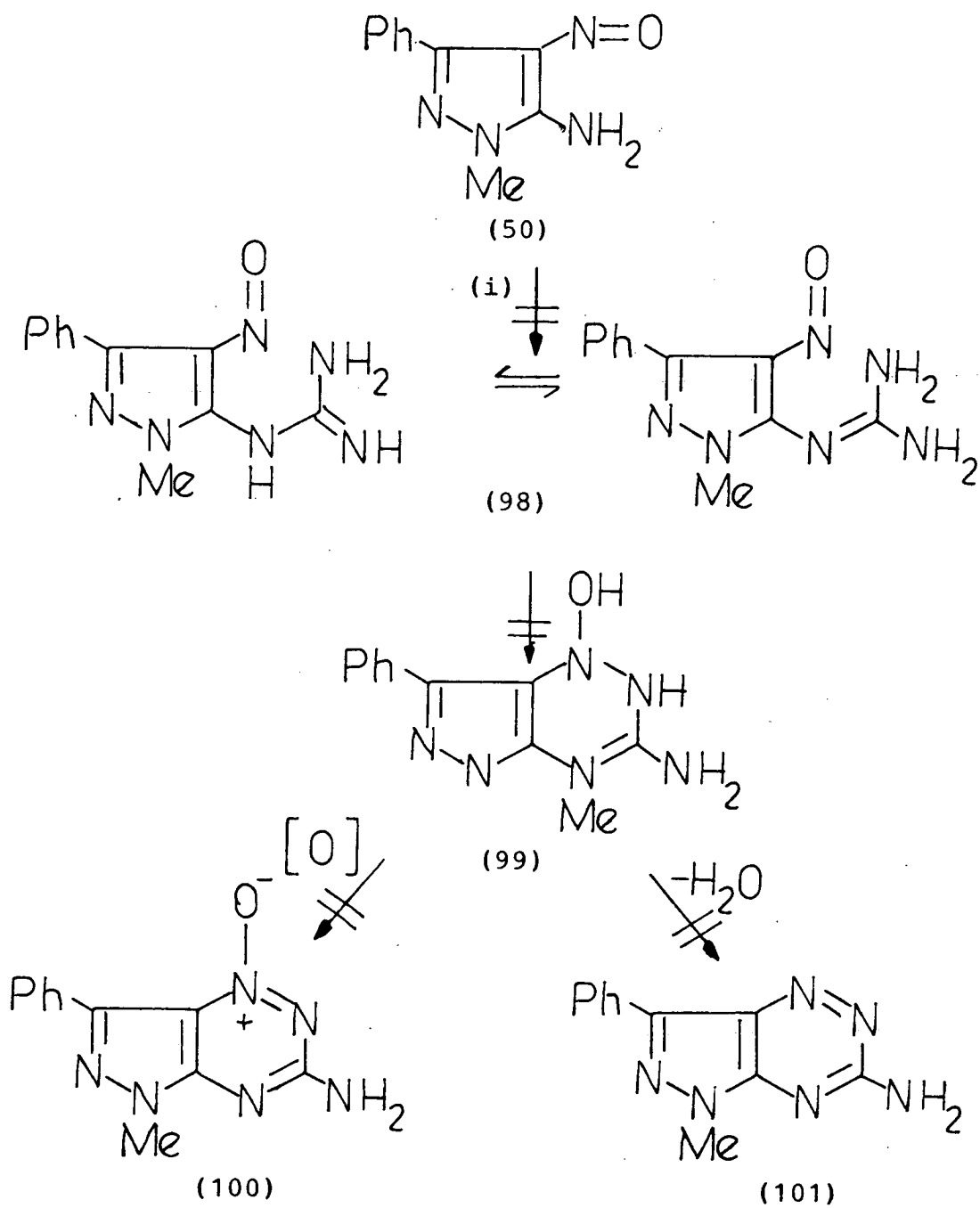
Lister, Manner and Timmis¹²⁰ have reported the potassium carbonate-catalysed cyclisation (Scheme 24) of pyrazoline-4,5-dione-4-thiosemicarbazones (88) to pyrazolo[3,4-e]-1,2,4-triazinethiones (89), which on methylation gave the methylthio derivatives (90) and by further reaction with benzylamine and morpholine the corresponding amino derivatives (91). These compounds have been evaluated¹²⁰ as antitumour agents. Elnagdi *et al.*¹²¹ and Kampchen¹²² have also investigated the synthesis of pyrazolo[3,4-e]-1,2,4-triazines from pyrazole precursors. However the synthesis of N-oxygenated pyrazolo[3,4-e]-1,2,4-triazines has not been reported in the literature to date and in view of the potentially interesting biological properties of such compounds it was decided to investigate methods for their synthesis. It was envisaged (Scheme 25) that the readily available^{106,107} amino-nitrosopyrazole derivatives (20) could provide pyrazolylacetamide derivatives (92) suitable for cyclisation to hitherto unknown pyrazolo[3,4-e]-1,2,4-triazine N-oxides (94). It was hoped that under basic conditions the pyrazolylacetamides (92) would undergo cyclisation to N-hydroxy intermediates (93) capable of *in situ* oxidation to pyrazolotriazine N-oxides (94) or dehydration to the parent pyrazolotriazines (95) depending on the cyclisation conditions employed.

The synthesis of guanidine derivatives by the reaction



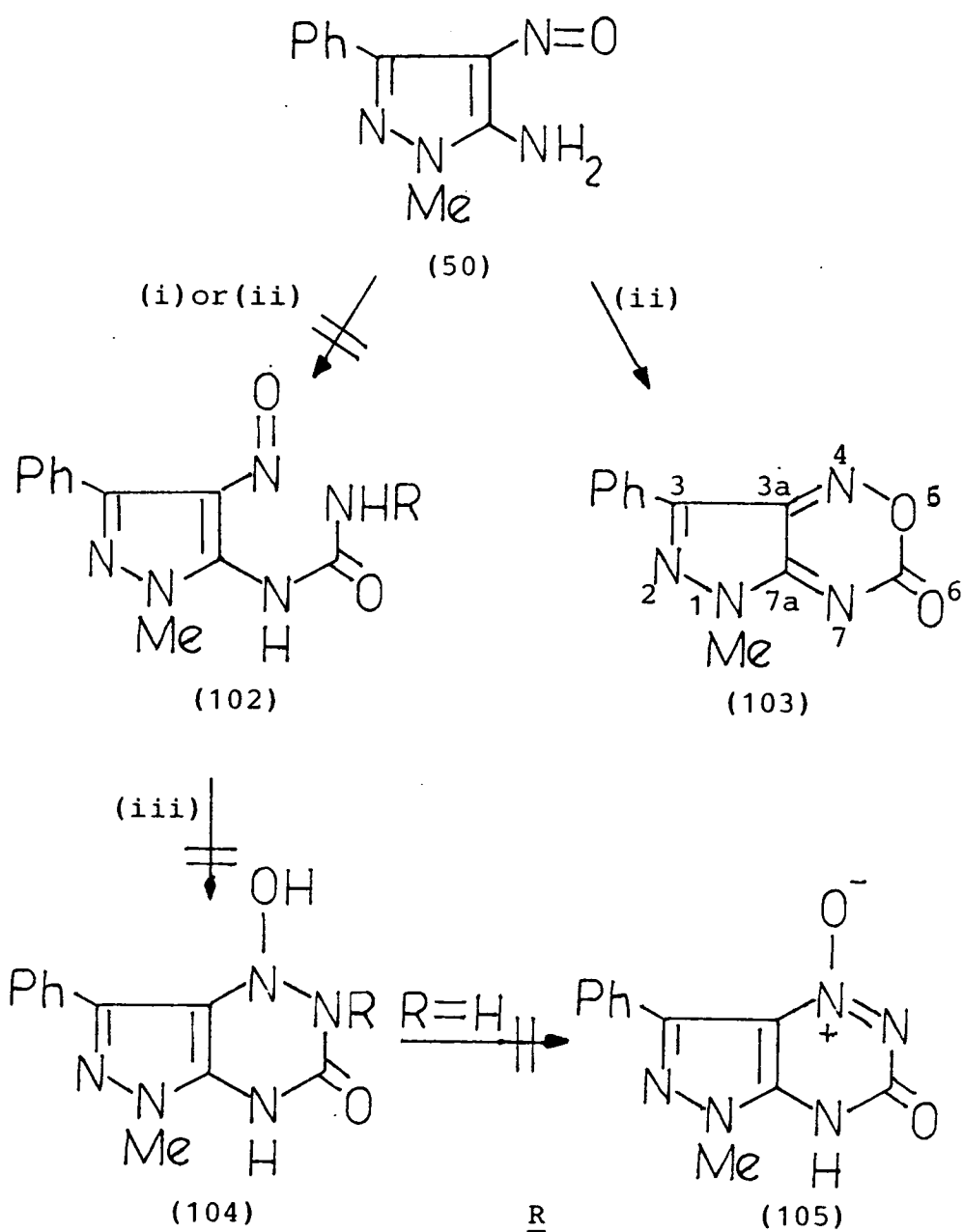
(i) NH_2CN , EtOH, heat.

Scheme 26



(i) NH_2CN , $\text{MeO}(\text{CH}_2)_2\text{OMe}$, heat.

Scheme 27



R
 a; Ph
 b; Me
 c; TSO₂ [T = p-MeC₆H₄]
 d; H

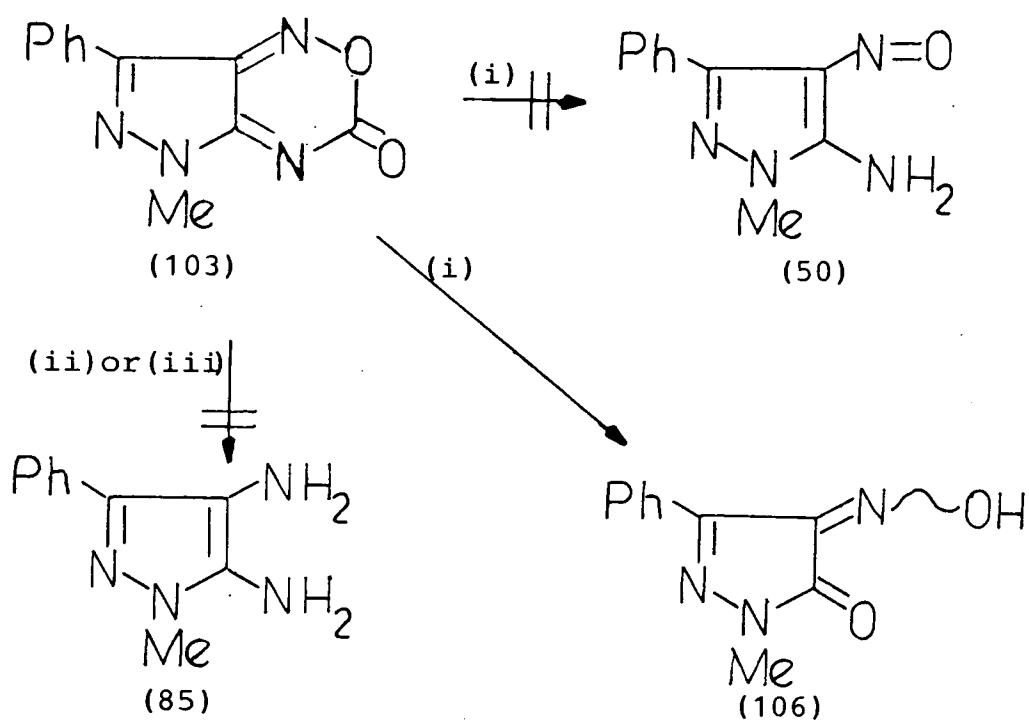
- (i) (H₂N)₂C=O, heat.
 (ii) RN=C=O, MeO(CH₂)₂OMe, heat.
 (iii) base.

Scheme 28

of aromatic amines with cyanamide is well known¹²³ and can be exemplified (Scheme 26) by the thermal reaction of cyanamide with *p*-bromoaniline hydrochloride (96) in ethanol, to give *p*-bromophenylguanidine (97).¹²⁴ Hence, it was decided to investigate the synthesis (Scheme 25) of pyrazolyl-guanidine derivatives (92; $R^3=NH_2$), potentially capable of cyclisation to the *N*-oxygenated pyrazolotriazines (94; $R^3=NH_2$). In practice (Scheme 27) heating the amino-nitrosopyrazole (50) with cyanamide in dry dioxane gave only a high recovery of unreacted pyrazole (50) and not the expected guanidine derivative (98). The failure of this reaction precluded the study of the cyclisation of the latter to the *N*-oxygenated pyrazolotriazine derivative (100).

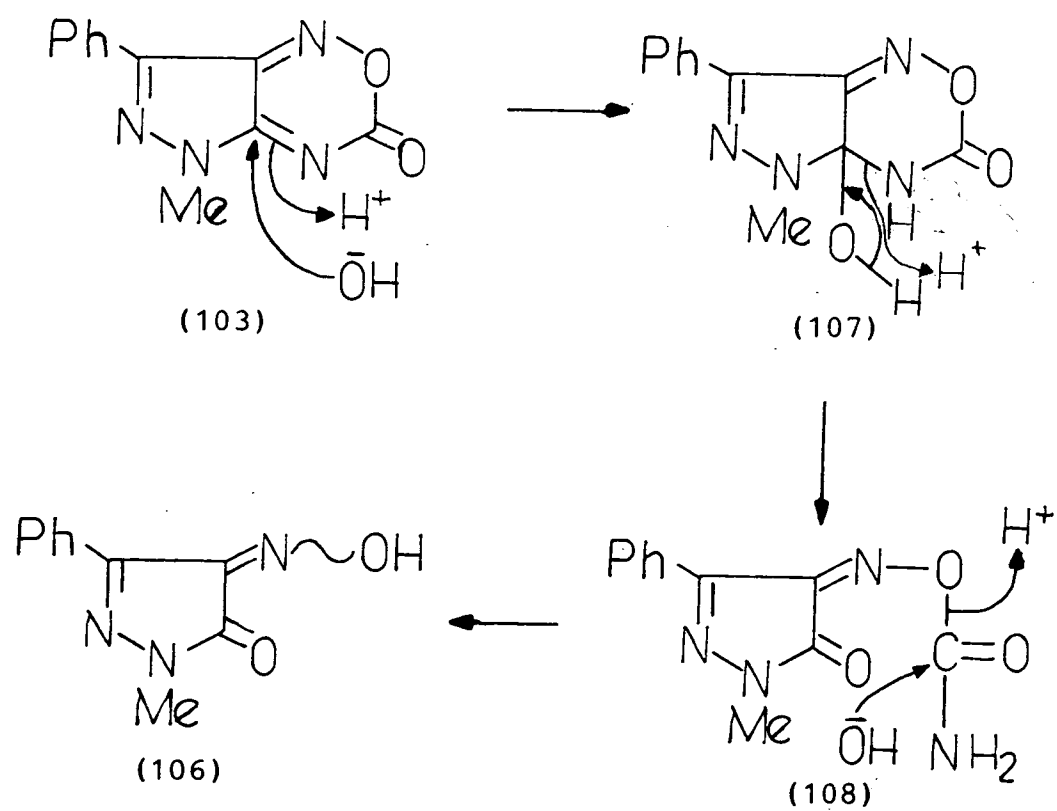
In view of the failure of the amino-nitrosopyrazole (50) to react with cyanamide an alternative approach to the synthesis of pyrazolo[3,4-*e*]-1,2,4-triazine *N*-oxides was examined. Thus, the synthesis (Scheme 25) of pyrazolyl-urea derivatives (92; $R^3=OH$) were investigated for subsequent base-catalysed cyclisation to *N*-oxygenated pyrazolotriazines (94; $R^3=OH$). The initial synthetic approach (Scheme 28) to the desired pyrazolyl-urea derivatives (102) involved the fusion of the amino-nitrosopyrazole (50) with urea. It is known¹²⁵ that aromatic amines when fused with urea give the corresponding substituted urea. However, fusion of the amino-nitrosopyrazole (50) with urea gave no product identifiable as the pyrazolyl-urea (102; $R=H$), only intractable mixtures being obtained.

An alternative approach (Scheme 28) to pyrazolyl-urea derivatives (102) involves the reaction of the amino-nitroso-



- (i) KOH, H₂O, EtOH, heat.
 (ii) H₂, Pd-C.
 (iii) NaBH₄, MeOH, H₂O, room temp.

Scheme 29



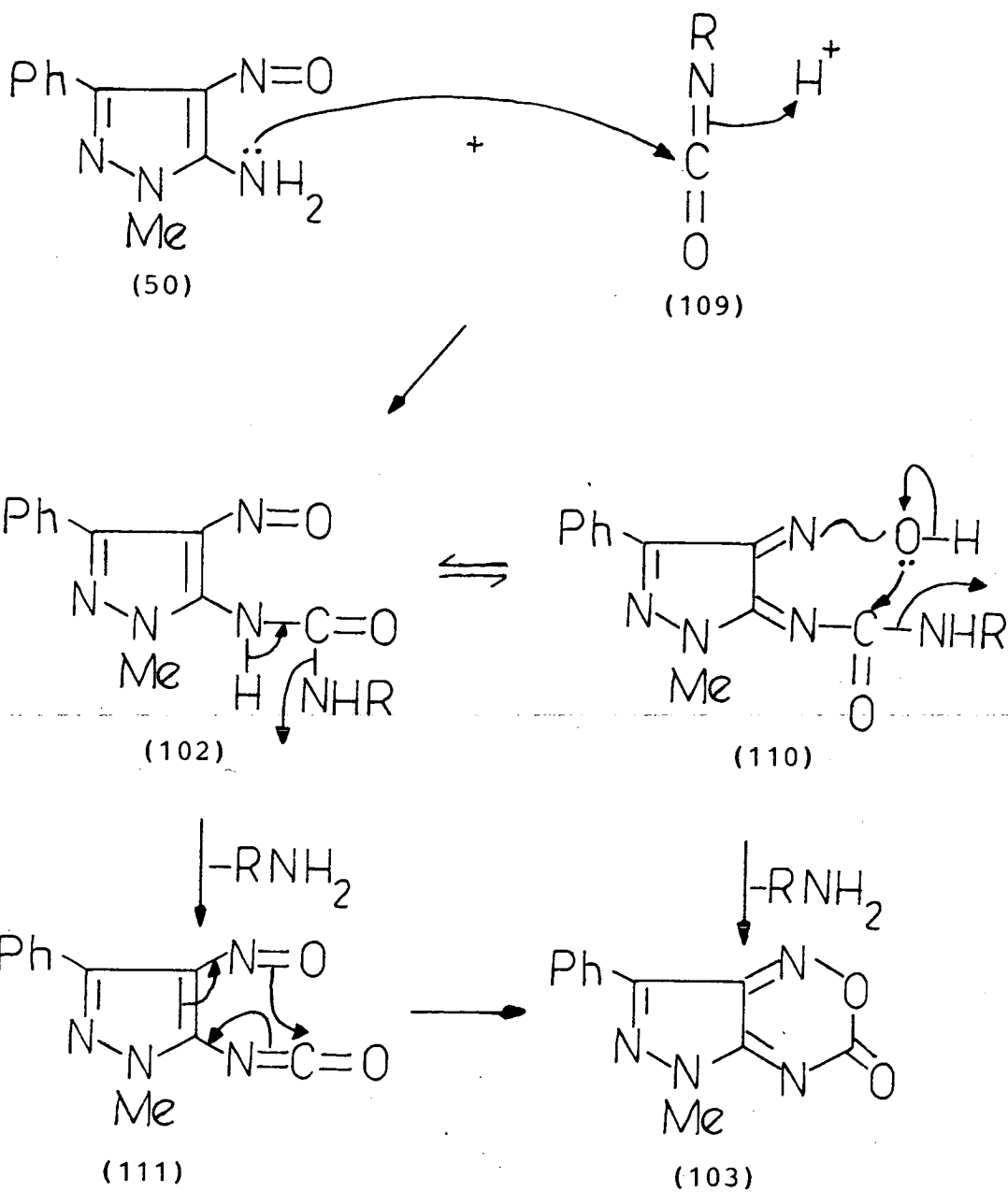
Scheme 30

pyrazole (50) with isocyanates. This approach could give urea derivatives (102; R≠H) capable of cyclisation to N-hydroxypyrazolo[3,4-e]-1,2,4-triazinones (104), though not pyrazolotriazinone N-oxides (105). The reaction of primary amines with isocyanates to give substituted ureas is well known in the literature.¹²⁶ In practice the reaction of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) with phenyl isocyanate under reflux in dry 1,2-dimethoxyethane gave only intractable mixtures and not the expected pyrazolylurea (102; R=Ph). Similarly the reaction of the amino-nitroso-pyrazole (50) with methyl isocyanate also failed to give a substituted urea derivative (102; R=Me). The observed product from the latter reaction, using a large excess of methyl isocyanate, was a red crystalline solid which gave analytical and mass spectral data consistent with the molecular formula $C_{11}H_8N_4O_2$. The i.r. spectrum of this product showed a high frequency carbonyl absorption at 1790 cm^{-1} and C=N absorption at 1635 cm^{-1} . The ^1H n.m.r. spectrum of the product showed only peaks due to the protons of a phenyl and an N-methyl substituent. These features are consistent with the pyrazolo [4,3-c]-1,2,5-oxadiazin-6-one structure (103). In particular the high frequency carbonyl absorption at 1790 cm^{-1} , is consistent with the lactone structure (103). Further evidence for the pyrazolo-oxadiazinone structure (103) was provided by the product's hydrolysis (Scheme 29) with aqueous ethanolic potassium hydroxide to give an orange-brown solid in high yield. The observed analytical and spectroscopic data for this product were consistent with the known¹²⁷ 1-methyl-4-oximino-3-phenyl- Δ^2 -pyrazolin-5-one structure (106).

It was also demonstrated that heating the amino-nitroso-pyrazole (50) in aqueous ethanolic potassium hydroxide gave only the unreacted starting-material (50), suggesting that the hydrolysis of the pyrazolo-oxadiazinone (103) to the oximinopyrazolinone (106) does not involve the amino-nitroso-pyrazole (50) as an intermediate. A possible mechanism (Scheme 30) for the hydrolysis of the pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) to the oximinopyrazolinone (106) therefore involves initial hydration of the N(7)-C(7a) imine bond in the oxadiazinone ring to give a hydroxy-intermediate (107), ring-opening of which would afford a pyrazolone derivative (108) prone to further hydrolysis to the oximinopyrazolinone (106).

In an attempt to gain further evidence (Scheme 29) for the pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one structure (103) its reduction to the known¹⁰² diaminopyrazole (85) was investigated. However the attempted catalytic hydrogenation or sodium borohydride reduction of the pyrazolo-oxadiazinone (103) afforded only intractable mixtures from which no identifiable material could be obtained.

The formation (Scheme 28) of the pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) from the amino-nitrosopyrazole (50) was shown to be very dependent on the reaction conditions employed. At room temperature no reaction was observed between the amino-nitrosopyrazole (50) and methyl isocyanate, and heating the amino-nitrosopyrazole (50) with an equimolar quantity of methyl isocyanate gave an unresolved mixture of the pyrazolo-oxadiazinone (103) and unreacted starting-material (50). It was only when the methyl isocyanate was



R

a; Ph

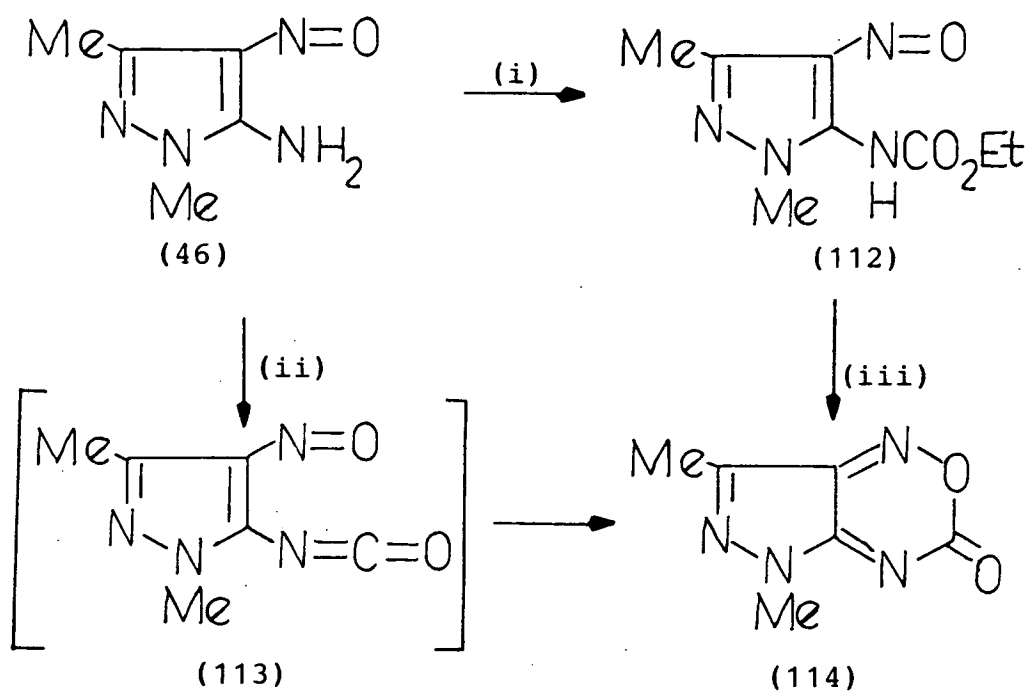
b; Me

c; TSO_2 [T = p-MeC₆H₄]

Scheme 31

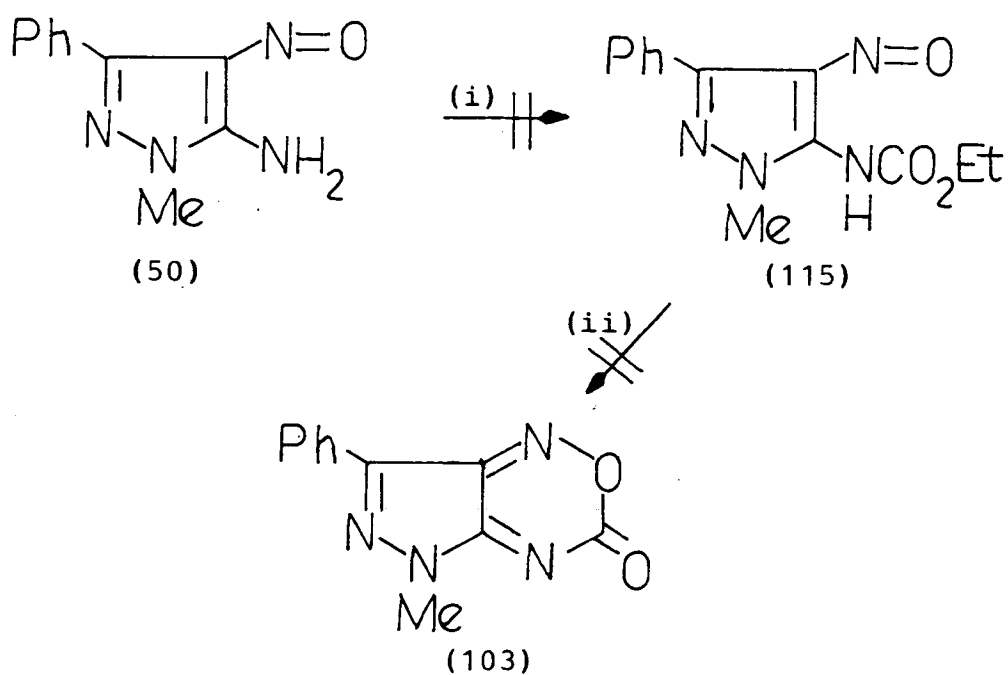
used in large excess that a moderate yield of the pyrazolo-oxadiazinone (103) was obtained. However, it was demonstrated that the yield of the pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) could be greatly improved by replacing methyl isocyanate with toluene-*p*-sulphonyl isocyanate (tosyl isocyanate) and that the latter did not have to be employed in more than 50% excess. The proposed mechanism for the formation of the pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) by reaction of the amino-nitrosopyrazole (50) with isocyanates is outlined in Scheme 31. The initial step probably involves the reaction of the amino-nitrosopyrazole (50) with the isocyanate (109) to give the expected urea derivative (102). However, this compound was never isolated and apparently (Scheme 31) undergoes spontaneous cyclisation to the pyrazolo-oxadiazinone (103) either through the intermediate formation and electrocyclisation of the pyrazolyl isocyanate (111) or alternatively by tautomerism to the oximino tautomer (110) followed by cyclisation involving intramolecular nucleophilic attack by the oximino substituent on the urea side-chain. Either of these mechanisms is supported by the higher yields of the oxadiazinone (103) obtained using tosyl isocyanate instead of methyl isocyanate, the urea intermediate (102c) produced in the former case being more prone to isocyanate formation or intramolecular nucleophilic cyclisation as a result of the superior leaving-group capacity of toluene-*p*-sulphonamide compared with methylamine.

The synthesis of pyrazolo[4,3-c]-1,2,5-oxadiazin-6-ones from amino-nitrosopyrazoles has already been reported in the literature.¹²⁸⁻¹³¹ Thus, Guarneri et al.¹³⁰ have demonstrated



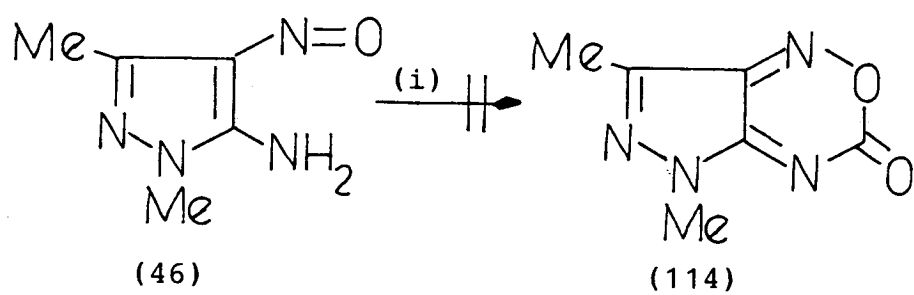
- (i) ClCO_2Et , CHCl_3 , NaHCO_3 , H_2O .
- (ii) COCl_2 , CHCl_3 , NaOAc .
- (iii) light petroleum, heat.

Scheme 32



- (i) ClCO_2Et , dioxane, Et_3N or ClCO_2Et , MeNCO , NaH .
- (ii) heat.

Scheme 33

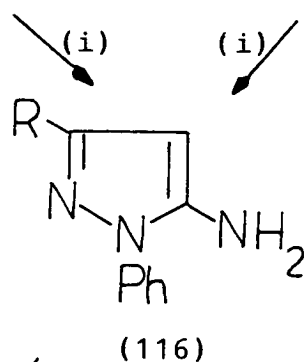
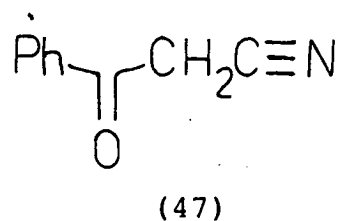
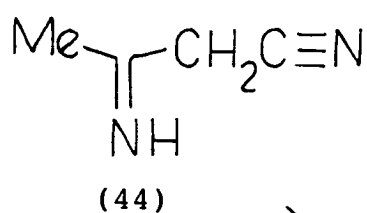


(i) $\text{MeN}=\text{C}=\text{O}$ or $\text{TSO}_2\text{N}=\text{C}=\text{O}$, $\text{MeO}(\text{CH}_2)_2\text{OMe}$, heat.
 [T = *p*-MeC₆H₄]

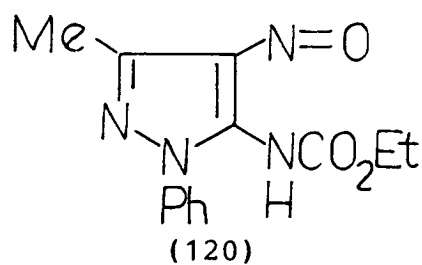
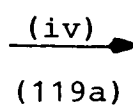
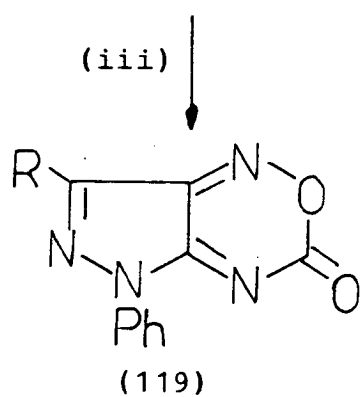
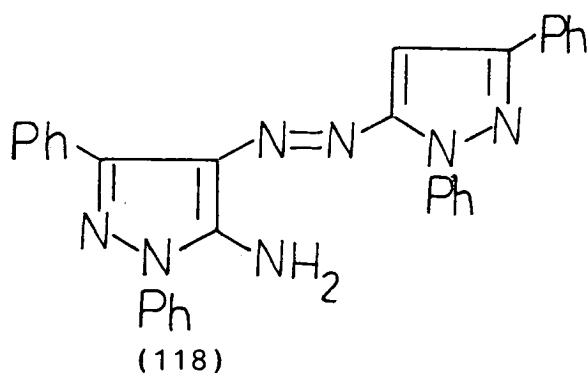
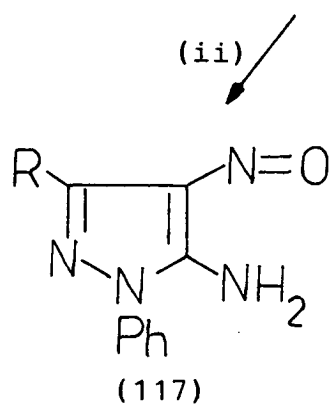
Scheme 34

(Scheme 32) the synthesis of the 1,3-dimethyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (114) by the reaction of the amino-nitrosopyrazole (46) with phosgene in good yield, presumably through the formation and electrocyclisation of the pyrazolyl isocyanate intermediate (113). It was further demonstrated (Scheme 32)¹³⁰ that reaction of the amino-nitrosopyrazole (46) with ethyl chloroformate afforded the urethane derivative (112), the thermolysis of which gave an excellent yield of the pyrazolo-oxadiazinone (114). By analogy with the work of Guarneri *et al.*¹³⁰ the synthesis (Scheme 33) of the novel 1-methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) was attempted in the present studies using ethyl chloroformate, the intention being to isolate the urethane (115) and to study its thermal cyclisation to the pyrazolo-oxadiazinone (103). In practice (Scheme 33) the reaction of the amino-nitrosopyrazole (50) with ethyl chloroformate failed to give the expected urethane (115). The reaction of the amino-nitrosopyrazole (50) with ethyl chloroformate in the presence of either triethylamine or sodium hydride as the basic catalyst afforded only complex mixtures rather than the hoped for urethane (115), thus preventing the proposed study of its thermal cyclisation to the pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103).

The synthesis of the pyrazolo-oxadiazinone (103) by the reaction of the amino-nitrosopyrazole (50) with isocyanates are novel processes and it was therefore of interest to investigate the generality of such transformations. Thus (Scheme 34) the readily available amino-nitrosopyrazole (46) was heated with methyl isocyanate in 1,2-dimethoxyethane in



R
a; Me
b; Ph

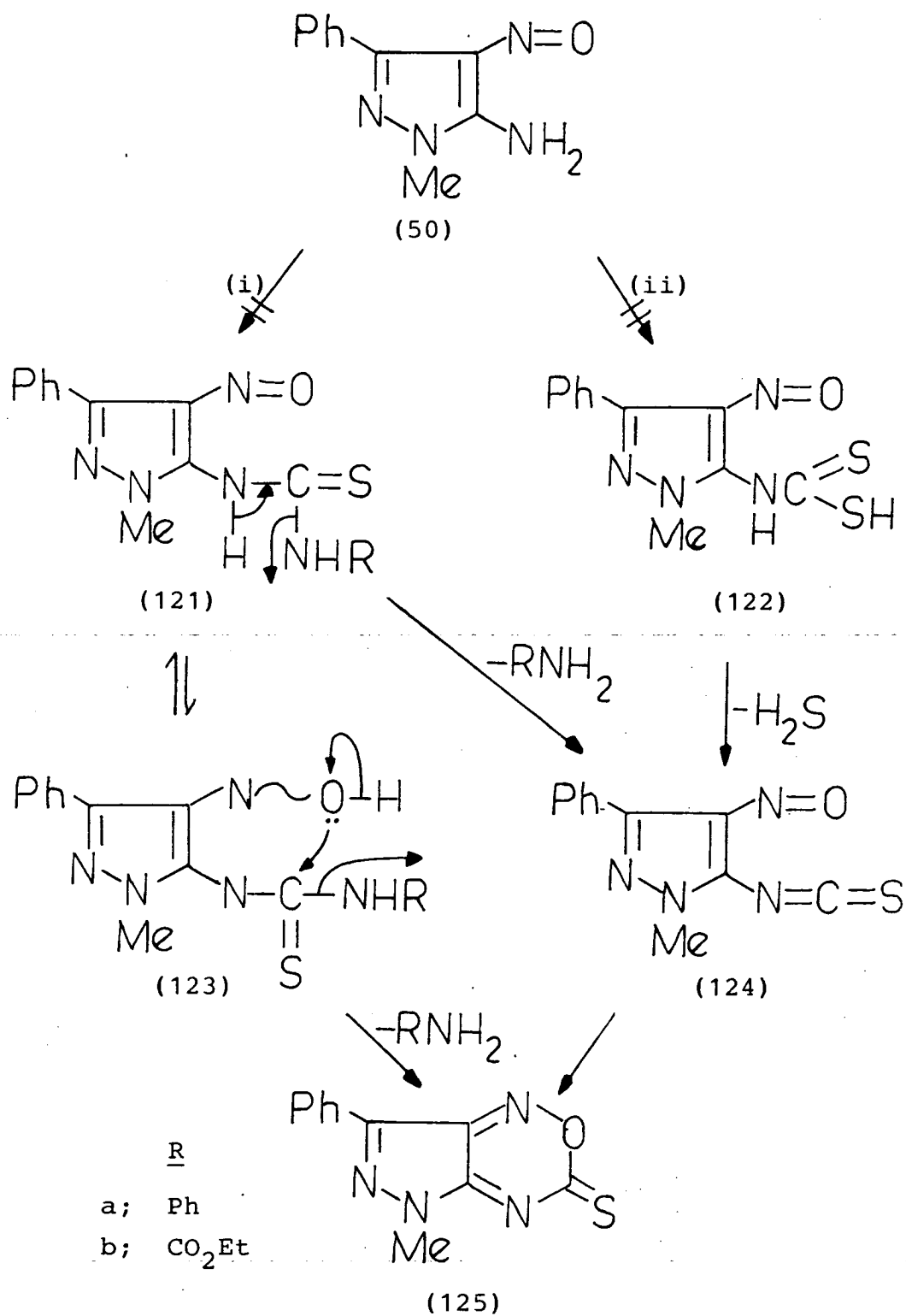


- (i) PhNHNH_2 , EtOH, heat.
(ii) NaNO_2 , H_2O , AcOH.
(iii) $\text{TSO}_2\text{N}=\text{C}=\text{O}$, $\text{MeO}(\text{CH}_2)_2\text{OMe}$, heat.
(iv) EtOH, heat.

the expectation of obtaining the dimethylpyrazolo-oxadiazinone (114) already described by Guarneri *et al.*¹³⁰ In practice this reaction gave only an intractable mixture which yielded no identifiable material. Heating the amino-nitrosopyrazole (46) with tosyl isocyanate in 1,2-dimethoxyethane was equally unsuccessful the product being an intractable gum. These disappointing results implied that the reaction of aminonitrosopyrazoles with isocyanates to give pyrazolo-oxadiazinones was not general in character. However the syntheses (Scheme 35) of the pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one derivatives (119) from the reactions of the corresponding amino-nitrosopyrazoles (117) with tosyl isocyanate were successful. Thus, heating 3-aminocrotononitrile (44) with phenylhydrazine in ethanol gave the expected aminopyrazole derivative (116a) in moderate yield. The spectroscopic properties of this compound were in accord with the assigned structure and the observed melting-point was close to the literature value.¹³² The reaction of the aminopyrazole derivative (116a) with sodium nitrite in aqueous acetic acid gave the known¹³³ 5-amino-3-methyl-4-nitroso-1-phenylpyrazole (117a) in good yield. This compound reacted readily when heated with tosyl isocyanate in 1,2-dimethoxyethane to give a low yield (37%) of the expected pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (119a). This known¹²⁸ compound had a melting-point close to the literature value and its analytical and spectroscopic properties were consistent with the assigned structure. In particular its i.r. spectrum contained high frequency carbonyl absorption at 1780 cm^{-1} typical of the lactone structure (119) (see before). A moderate yield of a

green gum was also isolated in the reaction of the amino-nitrosopyrazole (117a) with tosylisocyanate. This product gave accurate mass data consistent with the molecular formula $C_{13}H_{14}N_4O_3$ and its spectroscopic properties were in accord with the urethane structure (120). Thus its i.r. spectrum contained bands at 3360, 3260 and 1740 cm^{-1} due to the NH and ethoxycarbonyl components of a urethane substituent and its ^1H n.m.r. spectrum showed proton resonances characteristic of an ethyl substituent at $\delta 3.92$ and 1.07 in addition to signals due to the protons of a phenyl and a methyl group. The formation of the urethane (120) presumably results from the thermal reaction of the pyrazolo-oxadiazinone (119a) with ethanol used in the crystallisation of the crude product from the reaction of the amino-nitrosopyrazole (117a) with tosyl isocyanate.

The known¹³⁴ amino-diphenylpyrazole (116b) was readily prepared in high yield by the reaction of benzoylacetonitrile (47) with phenylhydrazine. However the C-nitrosation of the aminopyrazole (116b) under the usual conditions using sodium nitrite in aqueous acetic acid gave only a low yield (17%) of the known¹³⁵ amino-nitrosopyrazole derivative (117b). The major product of this reaction was a high melting solid whose melting-point was close to that reported¹³⁵ for the pyrazolyl-azopyrazole (118) also isolated by Cusmano¹³⁵ in the nitrosation of the aminopyrazole (116b). Heating the amino-nitrosopyrazole (117b) with tosyl isocyanate in 1,2-dimethoxyethane afforded a good yield of a red solid which gave analytical and mass spectral data consistent with the diphenylpyrazolo-[4,3-c]-1,2,5-oxadiazin-6-one structure (119b). In addition



(i) $\text{RN}=\text{C}=\text{S}$, $\text{MeO}(\text{CH}_2)_2\text{OMe}$, heat.

(ii) CS_2 , MeOH , heat.

Scheme 36

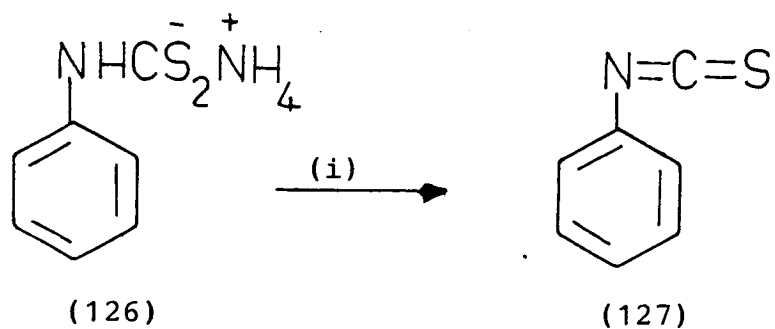
the i.r. spectrum of this product contained the expected high frequency carbonyl absorption at 1765 cm^{-1} associated with the lactone structure (119b).

The varying yields obtained in the synthesis (Scheme 35) of the pyrazolo[4,3-c]-1,2,5-oxadiazin-6-ones (119), demonstrates that their preparation by the reactions of the corresponding amino-nitrosopyrazoles (117) with tosyl isocyanate is dependent on the nature of the oxadiazinone product (119). The latter appear to be fairly reactive and can undergo nucleophilic ring-opening reactions, as demonstrated by the isolation of the urethane (120). Guarneri et al.¹²⁸ have also demonstrated the reactivity of pyrazolo[4,3-c]-1,2,5-oxadiazin-6-ones towards ring-opening to urethane derivatives and the general reactivity of pyrazolo[4,3-c]-1,2,5-oxadiazin-6-ones to nucleophilic ring-opening will be dealt with in detail later. The reactivity of the pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one ring system towards nucleophilic ring-opening may be a contributing factor in the failure (Scheme 34) of the amino-nitrosopyrazole derivative (46) to give the pyrazolo-oxadiazinone (114) when reacted with either methyl or tosyl isocyanate as described before.

Having demonstrated (Schemes 28 and 35) the novel synthesis of pyrazolo[4,3-c]-1,2,5-oxadiazin-6-ones by the reaction of ortho-amino-nitrosopyrazoles with isocyanates it was of interest to investigate the reaction of amino-nitrosopyrazole derivatives with isothiocyanates. The amino-nitrosopyrazole chosen for this study (Scheme 36) was the 1-methyl-3-phenyl derivative (50) and the expected product of the reaction of the latter with isothiocyanates was the

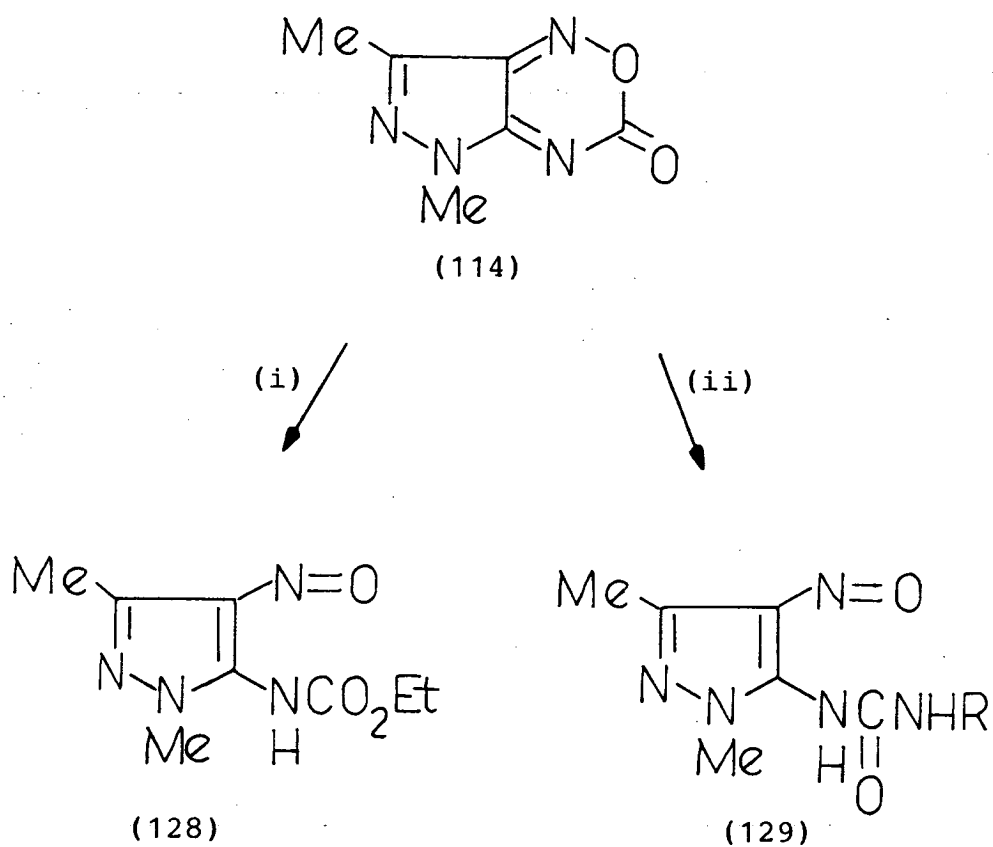
sulphur analogue of the pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103), pyrazolo[4,3-c]-1,2,5-oxadiazine-6-thione (125). It was anticipated (Scheme 36) that the initial reaction of the amino-nitrosopyrazole (50) with isothiocyanates would afford thioureas (121) which could yield the pyrazolo-oxadiazinethione (125) directly by tautomerism to the oxime intermediates (123) followed by cyclisation involving intramolecular nucleophilic attack by the oxime oxygen substituent on the thiourea side-chain with elimination of the elements of an amine. Alternatively the thiourea intermediate (121) might undergo thermal fragmentation to the isothiocyanate (124) electrocyclisation of which would then afford the pyrazolo-oxadiazinethione (125). In practice heating the amino-nitrosopyrazole (50) with phenyl isothiocyanate in 1,2-dimethoxyethane afforded only a quantitative recovery of the unreacted starting-material (50). Using the higher boiling dimethylformamide as the solvent, in an attempt to force the reaction of the amino-nitrosopyrazole (50) with phenyl isothiocyanate, only an intractable mixture, containing none of the expected pyrazolo-oxadiazinethione (125) was obtained. In a further attempt to obtain the pyrazolo-oxadiazinethione derivative (125) from the amino-nitrosopyrazole (50) the latter was heated under reflux with the commercially available ethoxycarbonyl isothiocyanate in the expectation of obtaining the intermediate thiourea (121b) and thence the pyrazolo-oxadiazinethione (125). However this reaction gave only an intractable mixture together with unreacted amino-nitrosopyrazole (50).

The reaction of amines with carbon disulphide is known¹³⁶



(i) $\text{Pb}(\text{NO}_3)_2, \text{H}_2\text{O}$.

Scheme 37



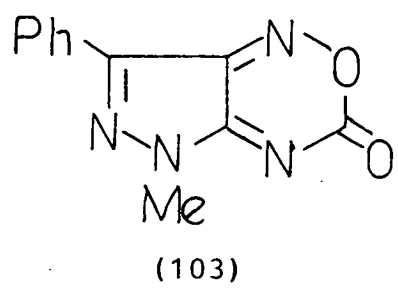
(i) EtOH , heat.
(ii) $\text{RNH}_2, \text{CHCl}_3$, room temp.

R
a; Ph
b; CH_2Ph

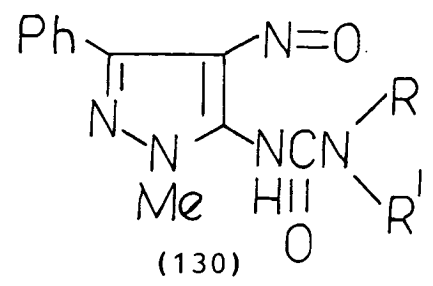
Scheme 38

to give dithiocarbamic acids which can be converted with loss of hydrogen sulphide into the corresponding isothiocyanates. Reactions of this type are exemplified (Scheme 37)¹³⁷ by the conversion of aniline on treatment with carbon disulphide into the ammonium salt of its phenyldithiocarbamic acid (126), subsequent decomposition of which affords phenyl isothiocyanate (127). It was thus of interest to investigate (Scheme 36) the reaction of the amino-nitrosopyrazole (50) with carbon disulphide in the hope of obtaining the pyrazolo-oxadiazinethione (125) via unstable dithiocarbamic acid and isothiocyanate derivatives (122) and (124). In practice however, heating the amino-nitrosopyrazole (50) with carbon disulphide in methanol gave only a high recovery of the amino-nitrosopyrazole (50) with no evidence for the formation of the pyrazolo-oxadiazinethione (125) or for that matter for the pyrazolecarbamic acid (122) or the pyrazole isothiocyanate (124).

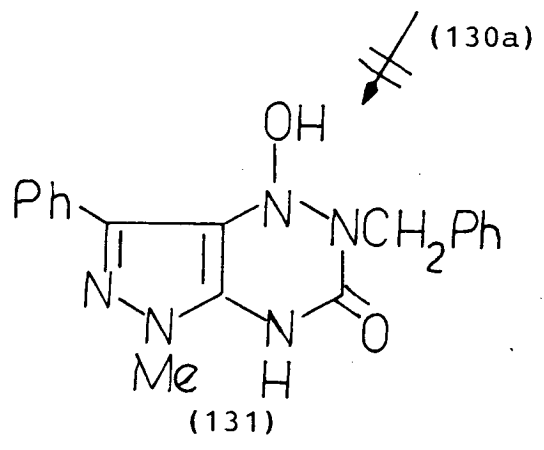
As mentioned before (see page 132) Guarneri *et al.*¹³⁰ have reported (Scheme 38) the ring-opening of the pyrazolo[4,3-*c*]-1,2,5-oxadiazin-6-one (114) to the urethane derivative (128), a reaction which occurs simply on heating the pyrazolo-oxadiazinone (114) with ethanol. These workers¹³⁰ further demonstrated (Scheme 38) the ring-opening of the pyrazolo-oxadiazin-6-one (114) with amines in chloroform at room temperature to the corresponding urea derivatives (129). It was therefore of interest to study analogous ring-opening reactions of the pyrazolo-oxadiazinone (103) synthesised in the present studies. The ring-opening of the pyrazolo-oxadiazinone (103) with amines (Scheme 39) was of particular interest



(i) →

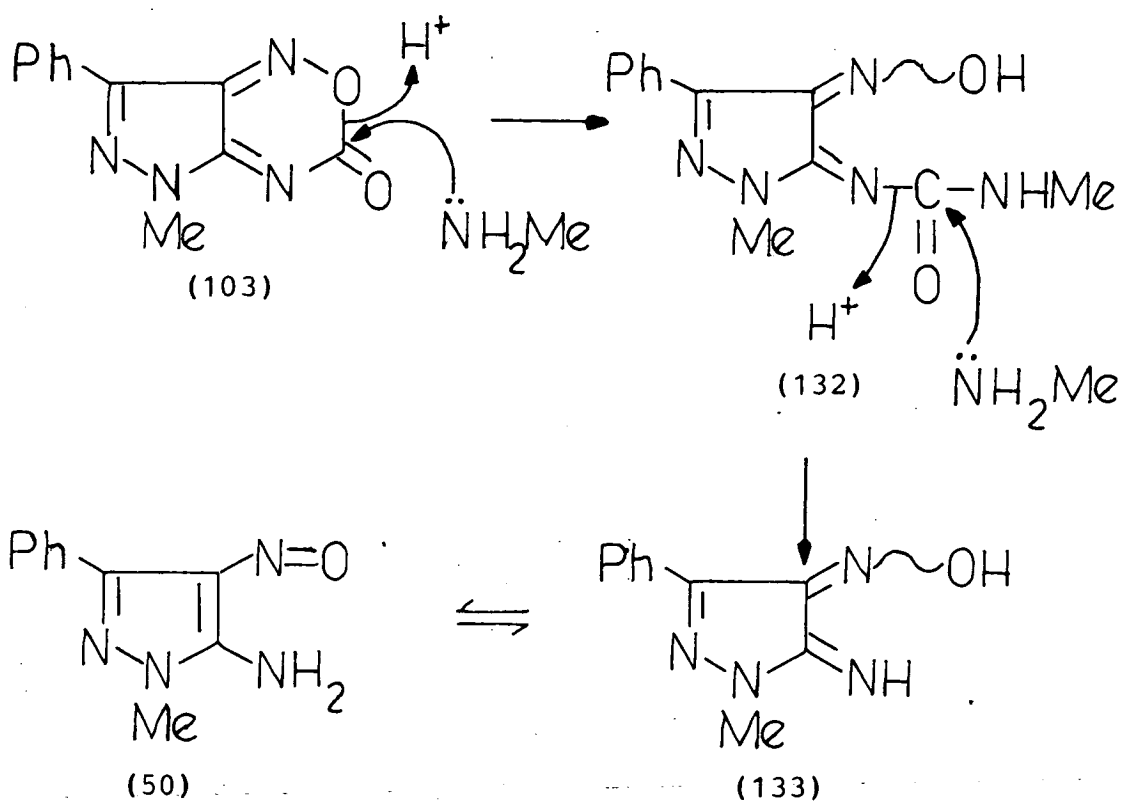


	<u>R</u>	<u>R'</u>
a;	CH ₂ Ph	H
b;	Et	Et
c;	CH ₂ Ph	Me
d;	-(CH ₂) ₄ -	
e;	-(CH ₂) ₅ -	
f;	-(CH ₂) ₂ O(CH ₂) ₂	

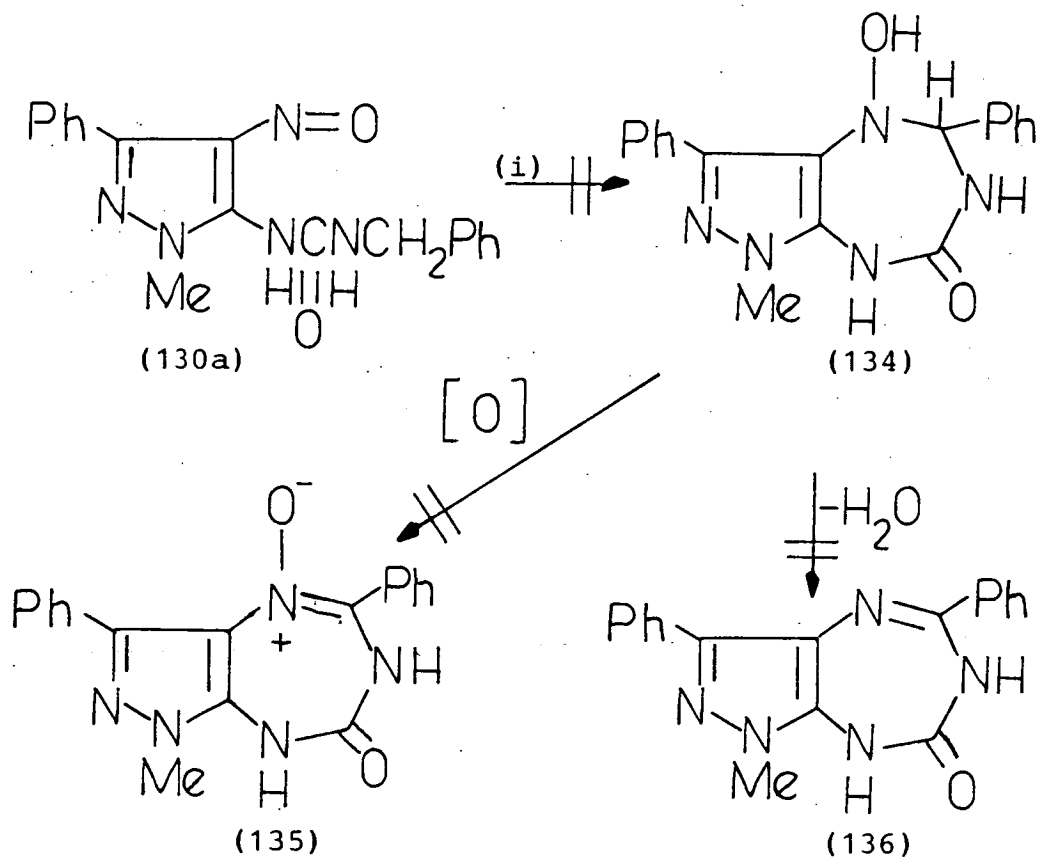


(i) RNHR¹, dioxane, room temp.

Scheme 39



Scheme 40



(i) NaOH , H_2O , heat.

Scheme 41

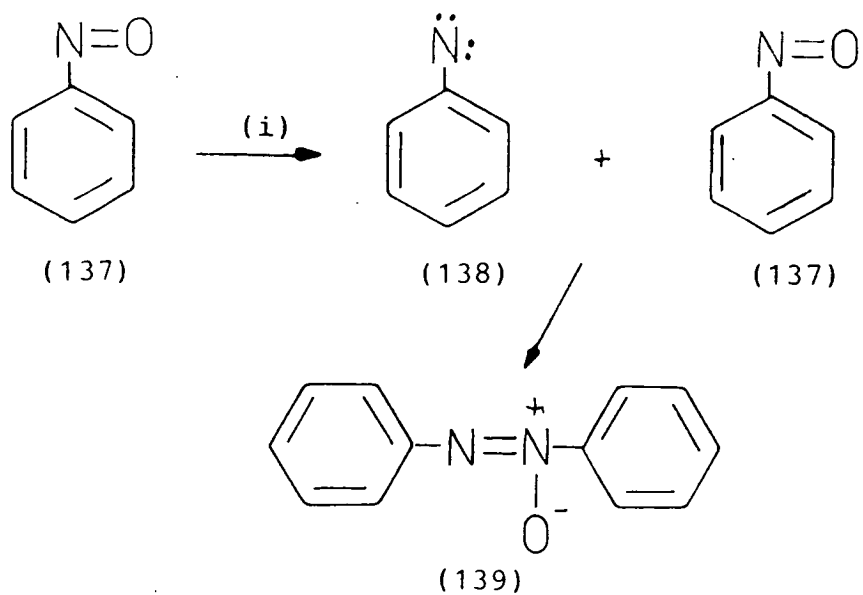
since certain of the resulting urea derivatives [e.g. (130a)] might spontaneously cyclise to the N-oxygenated pyrazolo-[3,4-e]-1,2,4-triazines [e.g. (131)] sought at the outset of the present studies of the reactions of amino-nitrosopyrazoles with isocyanates as already discussed in detail. Initially however it was found that reaction of the pyrazolo-oxadiazinone (103) with ethanolic methylamine did not give the expected pyrazolylurea derivative, the observed product (Scheme 40) being instead the amino-nitrosopyrazole (50). The formation of this product is presumably the result of the further aminolysis of the expected pyrazolylurea derivative (132) in the reaction medium as outlined in Scheme 40.

In contrast to the result with ethanolic methylamine, reaction (Scheme 39) of the pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) with benzylamine in dioxane at room temperature afforded a quantitative yield of a green crystalline solid which gave analytical and mass spectral data consistent with the molecular formula $C_{18}H_{17}N_5O_2$. The formulation of this compound as the expected urea derivative (130a) follows from its i.r. and 1H n.m.r. spectra. The former exhibits NH and carbonyl absorption at 3350 and 3300 and 1670 cm^{-1} attributable to a 1,3-disubstituted urea structure, while the latter shows proton resonances characteristic of a benzylamine derivative. Having obtained the benzylpyrazolylurea derivative (130a) it was of interest (Scheme 41) to investigate its behaviour towards reaction with base. It was hoped that the benzyl group in the pyrazolylurea (130a) might be acidic enough to undergo base-catalysed cyclisation across the adjacent nitroso-substituent to afford after in situ oxidation or dehydration

of the initially formed N-hydroxy intermediate (134), the interesting pyrazolotriazepinone N-oxide (135) and/or the parent pyrazolotriazepinone (136). By analogy with benzotriazepine derivatives¹³⁸ such compounds might possess interesting biological properties. In practice however, treatment of the benzylpyrazolylurea derivative (130a) with aqueous sodium hydroxide afforded only complex mixtures with no evidence for the formation of either pyrazolotriazepinone derivatives (135) or (136).

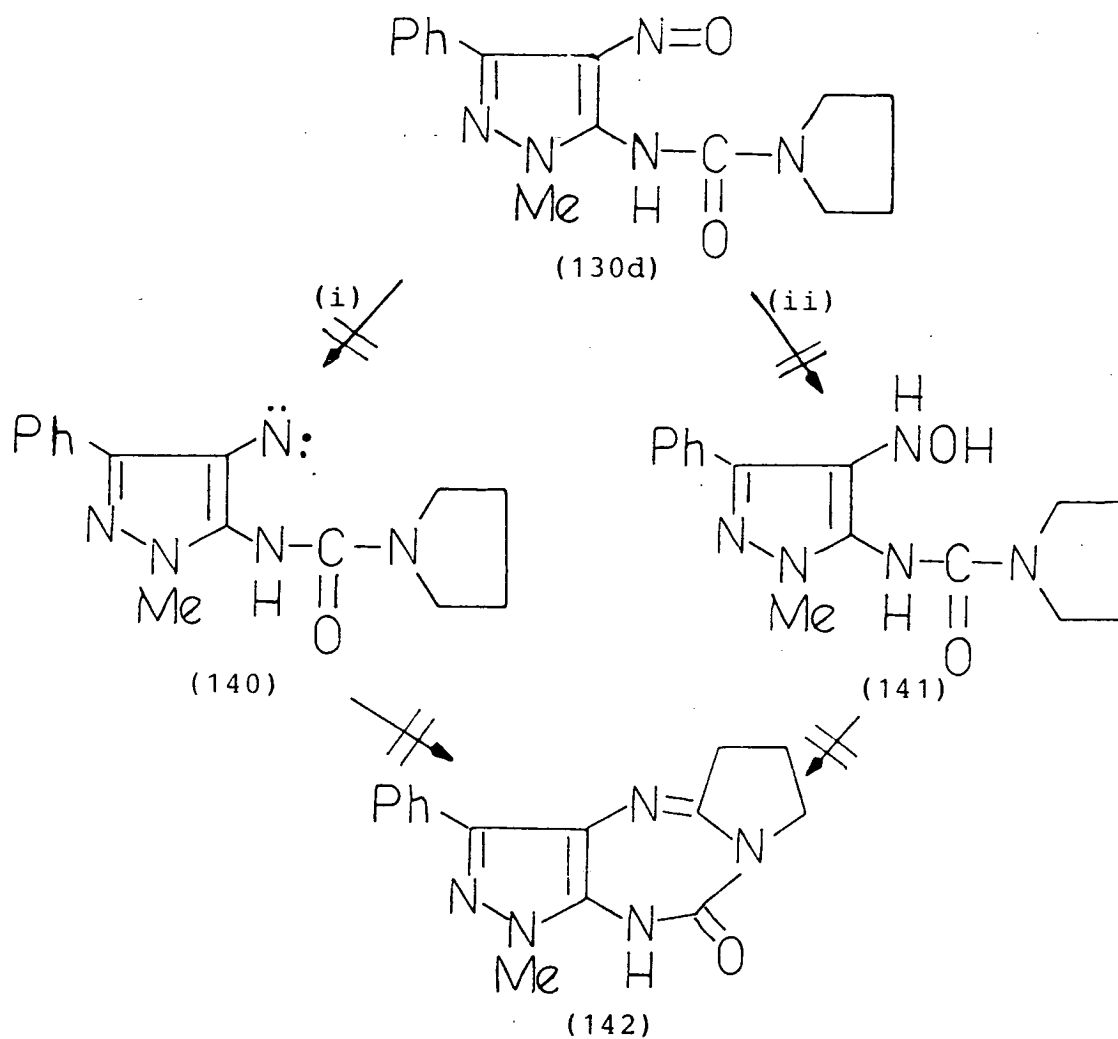
Having demonstrated (Scheme 39) the ring-opening of the pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one derivative (103) with the primary amine, benzylamine, it was of interest to study this reaction with secondary amines. Thus, treatment of the pyrazolo-oxadiazinone (103) with diethylamine in dioxane afforded a good yield of a green crystalline product whose analytical and spectroscopic properties are fully in accord with its formulation as the N,N-diethylurea derivative (130b). It was further demonstrated that the pyrazolo-oxadiazinone (103) also reacted with N-benzylmethylaniline to give the N-benzyl-N-methylurea derivative (130c) in moderate yield, together with some unreacted starting-material (103). The analytical and spectroscopic properties of the pyrazolylurea derivative (130c) were again entirely consistent with the proposed structure.

The reaction of the pyrazolo-oxadiazinone derivative (103) with cyclic secondary amines was also investigated. Treating the pyrazolo-oxadiazinone (103) with pyrrolidine in dioxane at room temperature gave an excellent yield of a green crystalline solid whose analytical and mass spectral data



(i) $(\text{EtO})_3\text{P}$, C_6H_6 , N_2 , 0° .

Scheme 42



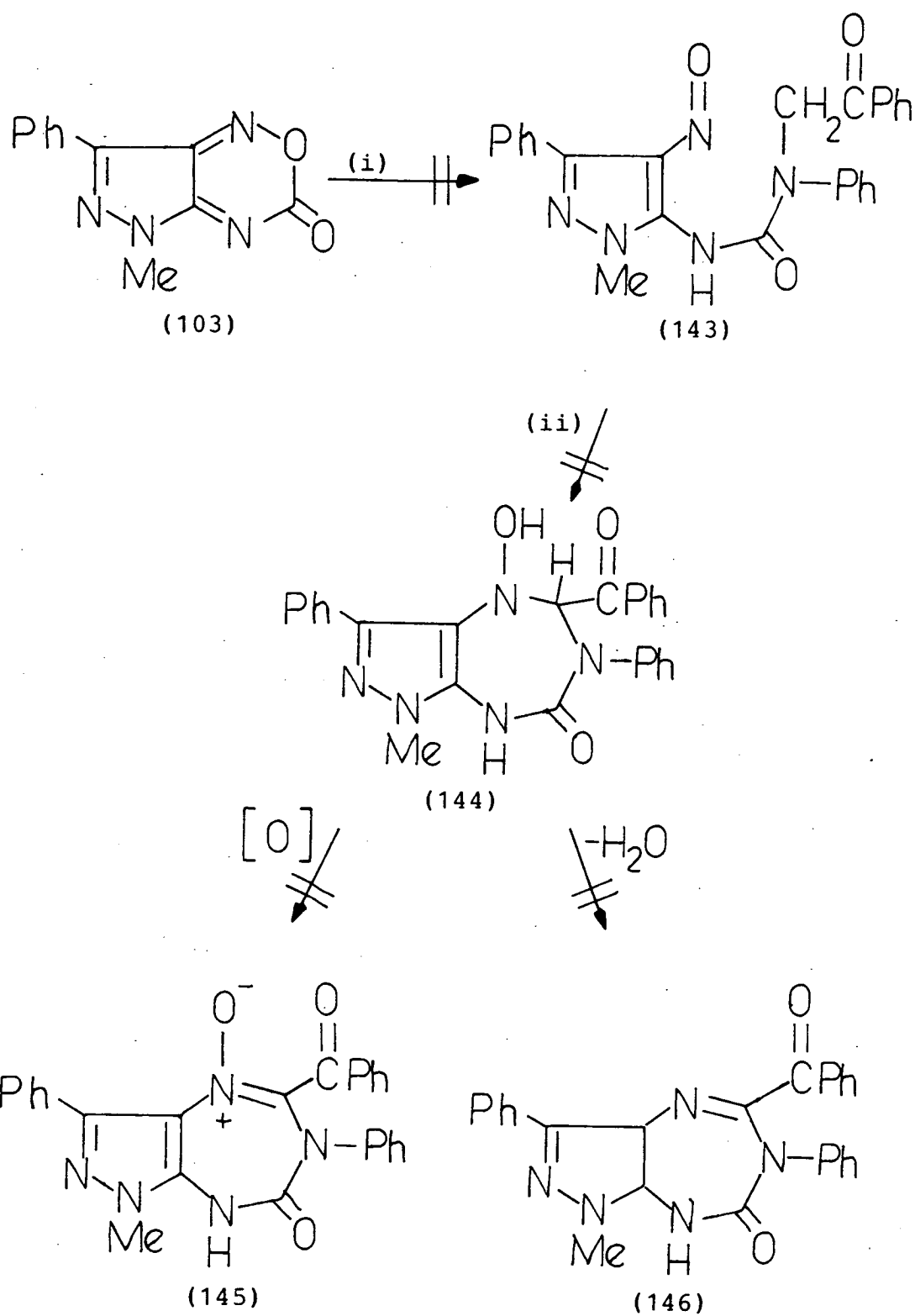
(i) $(\text{EtO})_3\text{P}$, C_6H_6 , heat.

(ii) $\text{Na}_2\text{S}_2\text{O}_4$, EtOH , H_2O , heat.

Scheme 43

were consistent with the N-substituted pyrrolidine structure (130d). This product also gave i.r. and ^1H n.m.r. spectral data fully in accord with the assigned structure (130d). However, reaction of the pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one derivative (103) with piperidine in dioxane failed to give the expected nitrosopyrazole derivative (130e). This reaction gave only a complex mixture from which no identifiable material could be obtained. On the other hand reaction of the pyrazolo-oxadiazinone (103) with morpholine in dioxane gave a high yield of a green crystalline product whose analytical and spectroscopic properties are entirely consistent with it being 4-[N-(1-methyl-4-nitroso-3-phenylpyrazol-5-yl)carbamoyl]-morpholine (130f).

Triethyl phosphite is known (Scheme 42)¹³⁹ to react with nitroso compounds [e.g. (137)] to effectively give a reactive radical species (138) which in the example shown reacts with the starting nitroso-compound (137) to give azoxybenzene (139) as the end-product. The ready availability of ortho-nitroso-pyrazolylurea derivatives (130) by ring-opening reactions of the pyrazolo-oxadiazinone (103) with amines as already described (see Scheme 39) prompted the study of their behaviour towards triethyl phosphite. Thus, (Scheme 43) in the specific case of the pyrrolidine derivative (130d), it was hoped that initial generation of the radical species (140) would be followed by insertion into the pyrrolidine ring to afford the fused pyrazolotriazepinone (142). However heating the nitrosopyrazole derivative (130d) with triethyl phosphite gave only a complex mixture which yielded no identifiable material. In an alternative approach (Scheme 43) to the tricyclic



(i) $\text{PhNHCH}_2\text{COPh}$, dioxane, room temp.

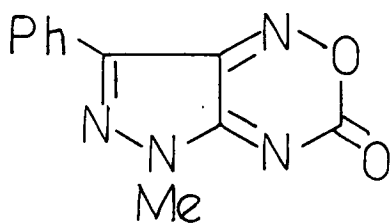
(ii) base.

Scheme 44

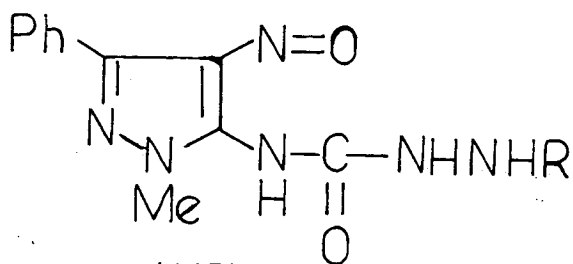
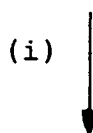
triazepinone (142) it was decided to attempt the reduction of the nitrosopyrazole (130d) to the hydroxylamine derivative (141) which might then be cyclodehydrated to the required compound (142). Unfortunately the attempted reduction of the nitrosopyrazole (130d) by heating with sodium dithionite in aqueous ethanol led only to a complex mixture and not the desired hydroxylamine intermediate (141), thus precluding the study of its cyclisation to the pyrazolotriazepinone (142).

Since the failure of the N-benzylpyrazolylurea (130a) to undergo base-catalysed cyclisation involving the nitroso-group (see page 135 and Scheme 41) could be attributed to the low acidity of the benzyl methylene substituent, hence leading to complex side-reactions rather than cyclisation, it was of interest to seek a more reactive substrate for cyclisation of this type. The compound chosen for study (Scheme 44) was the N-phenacylpyrazolylurea (143) which because of the expected enhanced acidic character of the methylene moiety of the phenacyl substituent should be prone to undergo base-catalysed cyclisation to the N-hydroxy intermediate (144) in situ oxidation or dehydration of which might then lead to the pyrazolotriazepinone derivatives (145) and/or (146). It was intended to obtain the required N-phenacylpyrazolylurea (143) by the nucleophilic ring-opening of the pyrazole-oxadiazinone (103) with N-phenacylaniline. However this reaction led only to a complex mixture from which no identifiable material could be obtained. This result precluded the study of the base-catalysed cyclisation of the N-phenacylpyrazolylurea (143).

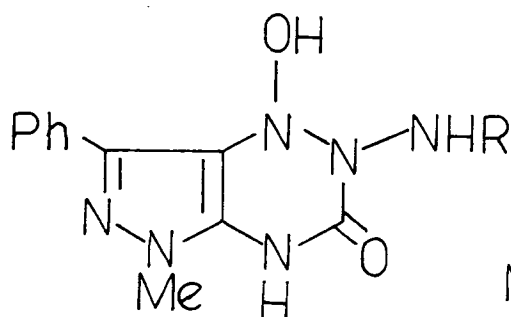
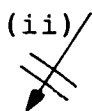
Having demonstrated ring-opening of the pyrazolo[4,3-c]-1,2,5-oxadiazinone (103) with primary and secondary amines to



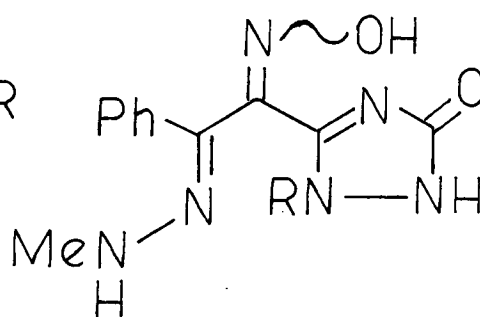
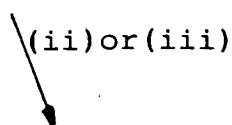
(103)



(147)



(148)



(149)

- (i) RNHNH_2 , dioxane, room temp.
 (ii) NaOH , H_2O , heat.
 (iii) EtOH , heat.

R

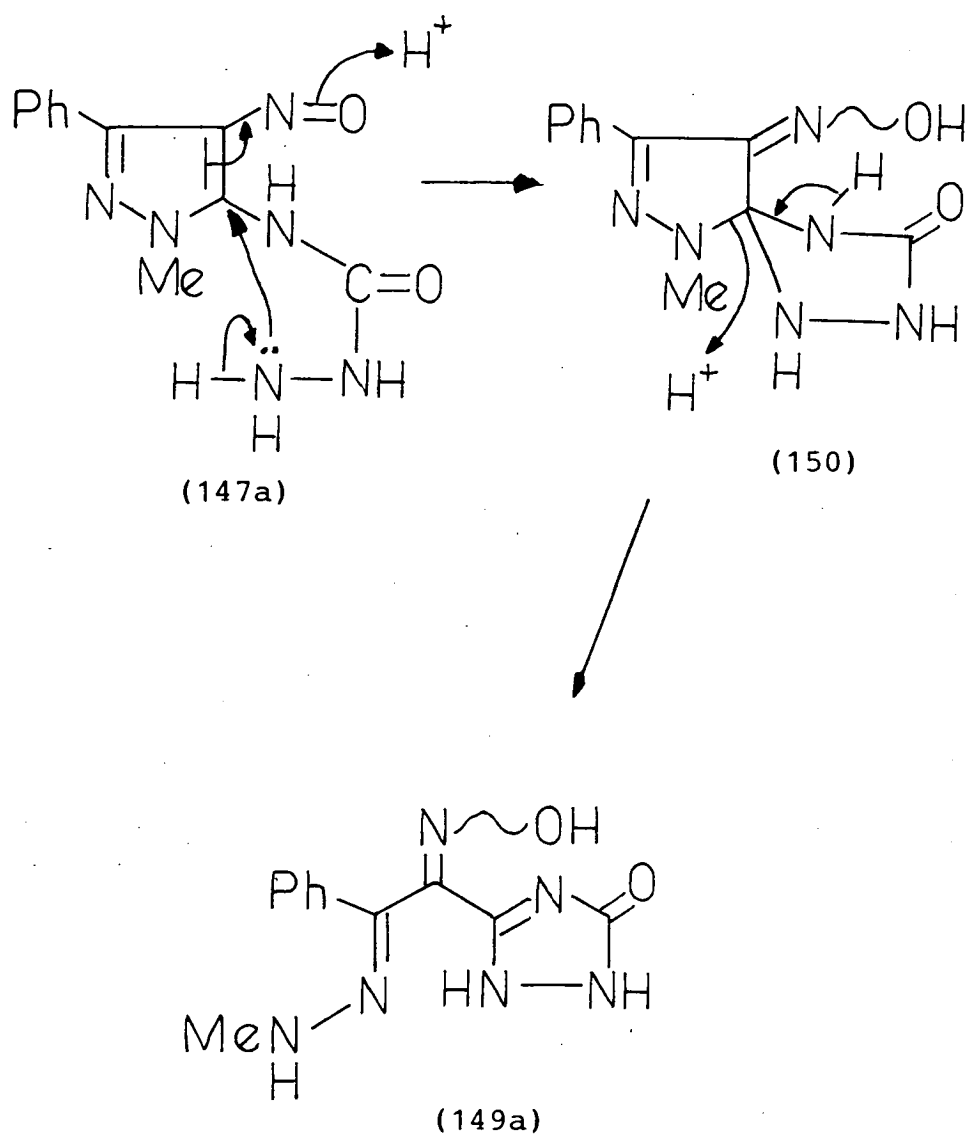
a; H

b; Ph

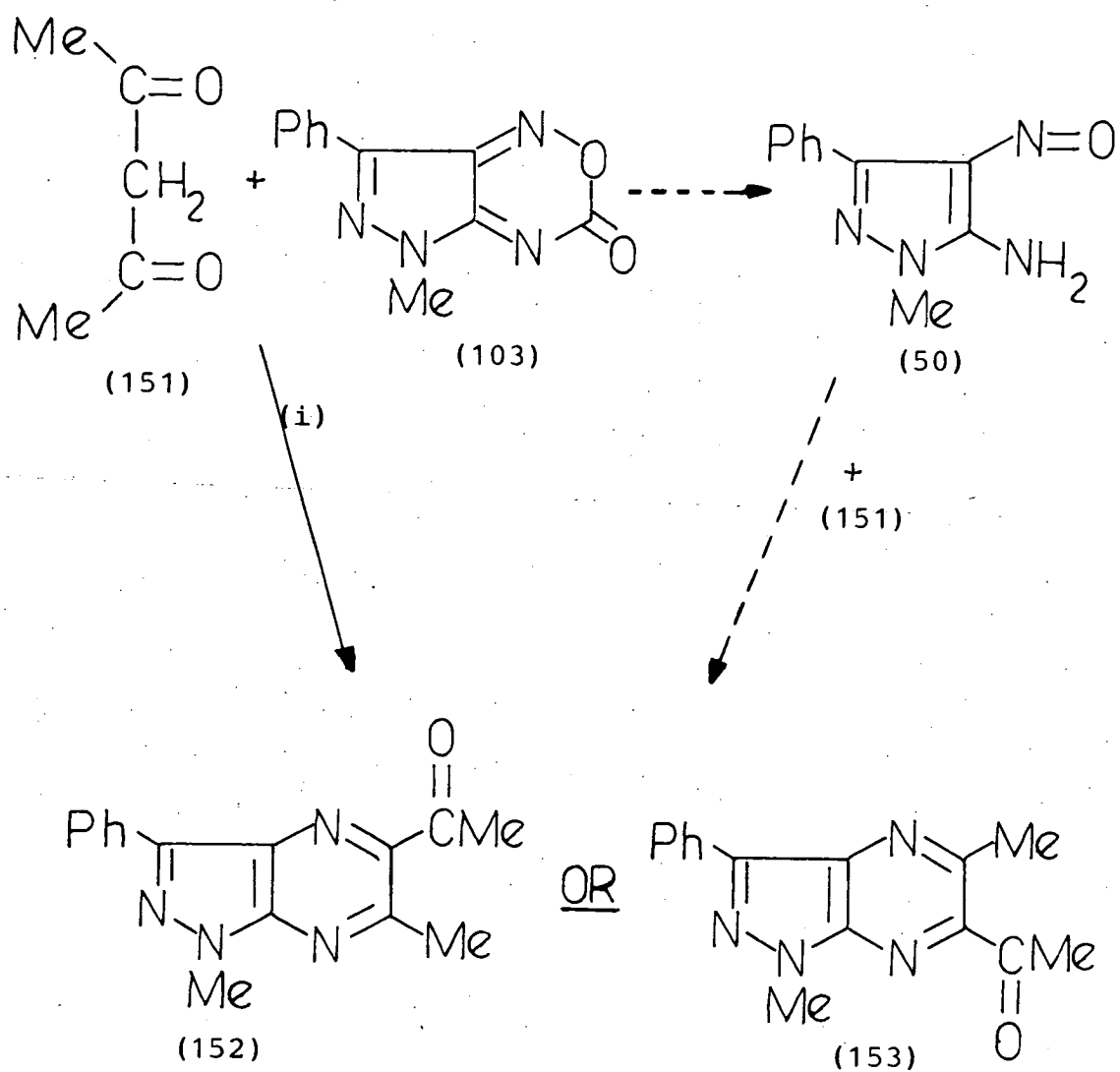
c; SO_2T

[T = p- $\text{H}_6\text{C}_6\text{M}$]

afford pyrazolylurea derivatives it was also of interest to study analogous nucleophilic ring-opening reactions with hydrazines. The expected products of such reactions (Scheme 45) were the pyrazolylcarbamoylhydrazine derivatives (147). The latter could potentially undergo base-catalysed cyclisation to N-oxygenated pyrazolo[3,4-e]-1,2,4-triazine derivatives (148), thus providing a further synthetic approach to the latter. In practice reaction of the pyrazolo-oxadiazinone (103) with hydrazine monohydrate in dioxane at room temperature gave a high yield of a green crystalline solid which could not be purified for combustion analysis because of its instability on attempted crystallisation. This compound failed to exhibit a parent ion on attempted mass spectral analysis but the presence of amino absorption in the i.r. spectrum and a carbonyl band at 1710 cm^{-1} allow its tentative formulation as the carbamoylhydrazine derivative (147a). Heating the suspected hydrazine derivative (147a) in ethanol gave a complex mixture, flash-chromatography of which afforded a low yield of a yellow crystalline solid. This product gave analytical and mass spectral data consistent with the molecular formula $\text{C}_{11}\text{H}_{12}\text{N}_6\text{O}_2$ and on the basis of its i.r. and ^1H n.m.r. spectra is tentatively formulated as the 1,2,4-triazolone derivative (149a). Thus its i.r. spectrum showed NH/OH absorption at $3450\text{--}2600\text{ cm}^{-1}$ and carbonyl absorption at 1730 cm^{-1} . In addition to proton resonances due to the phenyl substituent and the triazolone ring NH and oxime OH substituents the ^1H n.m.r. spectrum contained a one-proton quartet at $\delta 6.28$ and a three-proton doublet at $\delta 2.91$. Irradiation experiments allowed the assignment of these signals to the protons of an NHMe substituent demonstrating



Scheme 46



(i) Et_3N , dioxane, heat.

Scheme 47

that ring-opening of the pyrazole ring must have occurred. The possible mode of formation of the 1,2,4-triazolone derivative (149a) from the pyrazolylcarbamoylhydrazine (147a) is outlined in Scheme 46 and involves intramolecular nucleophilic attack by the hydrazine moiety at the 5-position of the pyrazole ring with subsequent ring-opening.

In an attempt to ascertain if the conversion of the pyrazolo-oxadiazinone (103) into pyrazolocarbamoylhydrazines (147) and further into 1,2,4-triazolone derivatives of the type (149) were general processes, it was decided to investigate the reactions of the pyrazolo-oxadiazinone (103) with other hydrazines. However, reaction of the pyrazolo[4,3-c]-1,2,5-oxadiazinone (103) with phenylhydrazine in dioxane at room temperature resulted in a complex mixture from which none of the pyrazolylcarbamoylhydrazine derivative (147b) could be obtained. On the other hand reaction of the pyrazolo-oxadiazinone (103) with toluene-*p*-sulphonylhydrazine (tosylhydrazine) afforded a good yield of a green crystalline solid whose analytical and spectroscopic properties were fully in accord with its formulation as the pyrazolylcarbamoyl-tosylhydrazine derivative (147c). Unfortunately the attempted base-catalysed conversion of this compound into the 1,2,4-triazolone derivative (149c) was unsuccessful, treatment with aqueous sodium hydroxide leading only to a complex mixture.

Finally, having demonstrated the ring-opening reactions of the pyrazolo-oxadiazinone (103) with both amines and hydrazines it was of interest (Scheme 47) to study its possible nucleophilic ring-opening with carbanionic reagents such as that derived from acetylacetone. In practice, heating the pyrazolo-oxadiazinone (103) with acetylacetone in dioxane in

the presence of triethylamine gave a low yield of a yellow solid whose analytical and mass spectral properties indicated the molecular formula $C_{15}H_{14}N_4O$. The i.r. spectrum of this product showed carbonyl absorption at 1690 cm^{-1} and its ^1H n.m.r. spectrum contained resonances characteristic of the protons of a phenyl substituent and three methyl groups. These features allowed the formulation of the yellow solid as one or other of the isomeric pyrazolopyrazine structures (152) or (153). The formation of either of these products (Scheme 47) requires the reaction of acetylacetone not with the pyrazolo-oxadiazinone (103) as hoped but rather with the amino-nitrosopyrazole (50) produced by its in situ solvolysis by the triethylamine catalyst. The solvolysis of the pyrazolo-oxadiazinone (103) to the amino-nitrosopyrazole (50) by ethanolic methylamine has already been described (see page 135). Further work will be required to fully establish which pyrazolopyrazine isomer (152) or (153) was obtained in the reaction of the pyrazolo-oxadiazinone (103) with acetylacetone in the presence of triethylamine.

(iii) ExperimentalBenzoylacetonitrile (47)

Benzoylacetonitrile (47) was prepared (yield 97%) by the reaction of 2-bromoacetophenone with potassium cyanide in aqueous ethanol at 45° as described by Obregia,¹¹¹ and had m.p. 69-72° (lit.,¹¹¹ 72-74°).

5-Amino-1-methyl-3-phenylpyrazole (48)

5-Amino-1-methyl-3-phenylpyrazole (48) was prepared (yield 65%) by the reaction of benzoylacetonitrile (47) with methylhydrazine as described by Tensmeyer and Ainsworth¹¹² and had m.p. 115-119° (lit.,¹¹² 129-131°).

5-Amino-1,3-dimethylpyrazole (45)

5-Amino-1,3-dimethylpyrazole (45) was prepared (yield 69%) by the reaction of β -aminocrotononitrile with methylhydrazine as described by Taylor and Hartke,¹⁰⁶ and had m.p. 60-65° (lit.,¹⁰⁶ 80-81°).

5-Amino-3-methyl-1-phenylpyrazole (116a)

A solution of 3-aminocrotononitrile (8.2 g, 0.1 mol) and phenylhydrazine (14.1 g, 0.13 mol) in absolute ethanol (25.0 ml) was heated under reflux for 17h. The mixture was evaporated and the residue was treated with aqueous 2M hydrochloric acid (100 ml) and extracted with methylene chloride to give a brown oil (5.8 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multi-component mixture which was not further investigated.

The aqueous phase was basified with solid sodium

hydroxide and the solid obtained was crystallised from toluene to give 5-amino-3-methyl-1-phenylpyrazole (116a) (9.6 g; 55%) m.p. 110-112° (lit., ¹³² 116°) ν_{\max} 3440, 3260 and 3130 (NH₂) and 1620 (C=N) cm⁻¹, δ (CDCl₃) 7.50-7.23 (5H, m, ArH), 5.36 (1H, s, pyrazole CH), 3.77 (2H, brs, NH₂) and 2.19 (3H, s, CH₃).

The toluene mother liquor was evaporated to give a gummy brown solid (0.57 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture, which was not further investigated.

Extraction of the basic aqueous mother liquor with methylene chloride gave a dark gum (3.0 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture from which no identifiable material could be obtained.

5-Amino-1,3-diphenylpyrazole (116b)

A solution of benzoylacetonitrile (13.7 g, 0.095 mol) and redistilled phenylhydrazine (10.3 g, 0.095 mol) in ethanol (40.0 ml) was heated under reflux for 17h. The mixture was evaporated and the residue triturated with ether to give 5-amino-1,3-diphenylpyrazole (116b) (20.1 g; 90%) m.p. 123-126° (lit., ¹³⁴ 129°), ν_{\max} 3420, 3300 and 3200 (NH₂) and 1630 (C=N) cm⁻¹.

5-Amino-1-methyl-4-nitroso-3-phenylpyrazole (50)

(a) A solution of 2-oximinobenzoylacetonitrile (49) ¹¹⁴ (8.7 g, 0.05 mol) and methylhydrazine (2.3 g, 0.05 mol) in ethanol (25.0 ml) was heated under reflux for 1h. The resulting suspension was filtered and the solid combined with

a second crop afforded by evaporating the ethanolic filtrate and triturating the red gum obtained with ethyl acetate, to give 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (total 4.6 g; 45%) m.p. 220-221°, identical (m.p. and i.r. spectrum) to a sample prepared in (b) later.

Evaporation of the ethyl acetate mother liquor gave a brown gum whose t.l.c. in ethanol over silica showed it to be an unresolvable multicomponent mixture, from which no further identifiable material could be obtained.

(b) 5-Amino-1-methyl-4-nitroso-3-phenylpyrazole (50) was prepared (yield 97%) by the reaction of 5-amino-1-methyl-3-phenylpyrazole (48) with sodium nitrite in aqueous acetic acid as described for the dimethyl-nitrosopyrazole (46) by Taylor and Hartke,¹⁰⁶ and had m.p. 217-220° (lit.,¹¹³ 230-231°).

5-Amino-1,3-dimethyl-4-nitrosopyrazole (46)

5-Amino-1,3-dimethyl-4-nitrosopyrazole (46) was prepared (yield 52%) by the reaction of 5-amino-1,3-dimethylpyrazole (45) with sodium nitrite in aqueous acetic acid as described by Taylor and Hartke,¹⁰⁶ and had m.p. 165-168° (lit.,¹⁰⁶ 169-171°).

5-Amino-3-methyl-4-nitroso-1-phenylpyrazole (117a)

A solution of 5-amino-3-methyl-1-phenylpyrazole (116a) (5.2 g, 0.03 mol) in glacial acetic acid (7.0 ml) was treated dropwise with stirring at 0-10° (ice-bath) with a solution of sodium nitrite (2.4 g, 0.035 mol) in water (12.0 ml) and the mixture was stirred at 0-10° for 1h. The resulting suspension was filtered and the solid well washed with ethanol to give

5-amino-3-methyl-4-nitroso-1-phenylpyrazole (117a) (4.4 g; 72%) m.p. 195-198° (decomp.) (lit., ¹³³ 200°) ν_{\max} 3300 (NH₂) and 1655 (C=N) cm⁻¹.

The ethanolic filtrate was evaporated to give a dark glassy solid (1.7 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture, which was not further investigated.

5-Amino-1,3-diphenyl-4-nitrosopyrazole (117b)

A solution of 5-amino-1,3-diphenylpyrazole (116b) (2.4 g, 0.01 mol) in glacial acetic acid (20.0 ml) was treated dropwise with stirring at 0-10° (ice-bath) with a solution of sodium nitrite (0.83 g, 0.012 mol) in water (4.0 ml) and the mixture stirred in the melting ice bath for 1h. The resulting suspension was filtered to give 5-(5-amino-1,3-diphenylpyrazol-4-yl)azo-1,3-diphenylpyrazole (118) (1.1 g) m.p. 200-204° (decomp.) (lit., ¹³⁵ 217°) ν_{\max} 3400 and 3280 (NH) cm⁻¹

The aqueous acetic acid filtrate was evaporated and the residue treated with water (5.0 ml) to give a solid which crystallised from ethanol to afford 5-amino-1,3-diphenyl-4-nitrosopyrazole (117b) (0.45 g; 17%) m.p. 195-198° (decomp.) (lit., ¹³⁵ 202-204°), ν_{\max} 3350, 3260 and 3190 (NH) and 1640 (C=N) cm⁻¹.

T.l.c. of the ethanolic mother liquor in methylene chloride over silica showed it to contain a complex mixture, which was not further investigated.

Reactions of 5-Amino-1,3-dimethyl-4-nitrosopyrazole (46) with Cyanoacetic Acid

(a) A solution of 5-amino-1,3-dimethyl-4-nitrosopyrazole

(46) (0.28 g, 0.002 mol) in dry methylene chloride (25.0 ml) was treated with cyanoacetic acid (0.18 g, 0.002 mol) and the resulting suspension was stirred at room temperature for 1h. The mixture was filtered to give the cyanoacetic acid salt of 5-amino-1,3-dimethyl-4-nitrosopyrazole (51) (0.39 g; 87%) m.p. 128-132° (decomp.), ν_{\max} 3360 (NH), 2260 (C≡N), 1740 br (CO) and 1655 (C=N) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.01 (2H, brs, NH_2), 3.83 (2H, s, CH_2), 3.40 (3H, s, NCH_3) and 3.50 (3H, s, CH_3).

Found : ($\text{M}^+ - \text{NCCH}_2\text{CO}_2\text{H}$), 140.

$\text{C}_8\text{H}_{11}\text{N}_5\text{O}_3$ requires: M, 225.

The salt (51) (0.25 g) was dissolved in hot water and the solution was basified with aqueous 2M sodium hydroxide solution, then neutralised with glacial acetic acid to give 5-amino-1,3-dimethyl-4-nitrosopyrazole (0.1 g) m.p. 155-160°, identical (m.p. and i.r. spectrum) to an authentic sample.

(b) Solutions of cyanoacetic acid (0.18 g, 0.002 mol) in dry methylene chloride (5.0 ml), dicyclohexylcarbodiimide (0.47 g, 0.0022 mol) in dry methylene chloride (5.0 ml) and 5-amino-1,3-dimethyl-4-nitrosopyrazole (46) (0.28 g, 0.002 mol) in dry methylene chloride (25.0 ml) were mixed and the mixture stirred at room temperature with protection from atmospheric moisture for 1h. The resulting green suspension was filtered and the solid obtained was washed with aqueous 2M sodium hydroxide solution (3.0 ml) and combined with a second crop obtained by evaporating the methylene chloride mother liquor, treating the residue with aqueous 2M sodium hydroxide solution (5.0 ml) and ethyl acetate, and filtering the resulting three phase system, to give dicyclohexylurea

(0.31 g) m.p. 224-225°, identical (m.p. and i.r. spectrum) to an authentic sample.

The combined aqueous alkaline mother liquors were acidified with concentrated hydrochloric acid and extracted with methylene chloride. The resulting three phase system was filtered to give 5-cyano-1,3-dimethylpyrazolo[3,4-b]-pyrazin-6(7H)-one (53) (0.1 g; 26%) which formed yellow crystals m.p. 260-265° (decomp.) (from ethanol) ν_{\max} 3480 br (NH), 2240 (C≡N) and 1680 br (CO) cm^{-1} .

Found: M^+ , 189.0649

$C_8H_7N_5O$ requires: M , 189.0651

The ethyl acetate mother liquor was evaporated to give a glassy brown solid (0.25 g) whose t.l.c. in methylene chloride showed it to be a multicomponent mixture, which was not further investigated.

The methylene chloride mother liquor was evaporated to give an intractable gummy brown solid (0.095 g) which was not further investigated.

(c) Solutions of cyanoacetic acid (0.34 g, 0.004 mol) in dry methylene chloride (10.0 ml), dicyclohexylcarbodiimide (0.94 g, 0.0044 mol) in dry methylene chloride (5.0 ml), and 5-amino-1,3-dimethyl-4-nitrosopyrazole (46) (0.56 g, 0.004 mol) in dry methylene chloride (50.0 ml) were mixed and the mixture stirred at room temperature with protection from atmospheric moisture for 3h. The resulting suspension was evaporated and the residue was subjected to column chromatography over silica.

Elution with methylene chloride-ether (9:1) gave a gummy solid which was triturated with methylene chloride-light

petroleum to afford dicyclohexylurea (0.14 g) m.p. 224-227°, identical (m.p. and i.r. spectrum) to an authentic sample. Evaporation of the methylene chloride-light petroleum mother liquor afforded a residue which was triturated with light petroleum to give a product tentatively formulated as O-(cyanoacetyl)-N,N'-dicyclohexylisourea (54) (0.095 g; 8%) which formed colourless crystals m.p. 73-75° (from toluene-light petroleum), ν_{\max} 3300 (NH), 2260 and 2180 (C≡N), 1715 (CO) and 1650 (C=N) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.27 (1H, brs, NH), 3.83 (2H, s, CH_2) and 1.93-1.19 (20H, brm, cyclohexane ring H).

Found: M^+ , 291.1885.

$\text{C}_{16}\text{H}_{25}\text{N}_3\text{O}_2$ requires: M, 291.1947.

Elution with methylene chloride-ether (4:1) afforded a further crop of dicyclohexylurea (0.25 g) m.p. 225-227°, identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with ether-ethyl acetate (1:1) afforded a gummy green solid which was triturated with ethanol-light petroleum to give 5-(α -cyanoacetamido)-1,3-dimethyl-4-nitrosopyrazole (52) (0.025 g; 3%) which formed green crystals m.p. 140-142° (from toluene-ethanol), ν_{\max} 3300 (NH) and 1700 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 4.13 (1H, s, NH), 3.66 (3H, s, NCH_3) and 2.28 (3H, s, CH_3).

Found: M^+ , 207.0752.

$\text{C}_8\text{H}_9\text{N}_5\text{O}_2$ requires: M, 207.0756.

Elution with ethyl acetate-ethanol (9:1) afforded unreacted 5-amino-1,3-dimethyl-4-nitrosopyrazole (46) (0.19 g; 34%) m.p. 153-156°, identical (m.p. and i.r. spectrum) to an authentic sample.

Reactions of 5-Amino-1-methyl-4-nitroso-3-phenylpyrazole

(50) with Cyanoacetic Acid

(a) A solution of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (2.0 g, 0.01 mol) and cyanoacetic acid (0.85 g, 0.01 mol) in dry methylene chloride (400 ml) was stirred and treated, with exclusion of atmospheric moisture, with a solution of dicyclohexylcarbodiimide (2.3 g, 0.011 mol) in dry methylene chloride (25.0 ml). The mixture was stirred at room temperature for 1h and the resulting green suspension was then evaporated and the residue treated with aqueous 2M sodium hydroxide (30.0 ml). The insoluble solid was collected, heated under reflux with water (20.0 ml) and the suspension filtered to give dicyclohexylurea (2.0 g) m.p. 216-218°, identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous extract was combined with the aqueous alkaline mother liquor and acidified with concentrated hydrochloric acid to afford 5-cyano-1-methyl-3-phenylpyrazolo[3,4-b]pyrazin-6(7H)-one (58) (2.1 g; 88%), which formed yellow crystals m.p. 316-317° (from ethanol-dimethylformamide), ν_{\max} 3100-2700 br (NH), 2230 (C≡N) and 1655 (CO) cm^{-1} , δ [(CD₃)₂SO] 8.20-8.21 (2H, m, ArH), 7.50-7.70 (3H, m, ArH) and 3.89 (3H, s, NCH₃).

Found: M^+ , 251.0804

C₁₃H₉N₅O requires: M , 251.0807

(b) A solution of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (0.40 g, 0.002 mol) and cyanoacetic acid (0.18 g, 0.002 mol) in dry methylene chloride (100 ml) was mixed with a solution of dicyclohexylcarbodiimide (0.46 g, 0.0022 mol) in dry methylene chloride (5.0 ml) and the mixture was

stirred with exclusion of atmospheric moisture at room temperature for 3h. The resulting suspension was evaporated and the residue suspended in water (20.0 ml), stirred, and treated with manganese dioxide (5.0 g) followed by dropwise addition of aqueous 2M sodium hydroxide solution (10.0 ml). The mixture was stirred at room temperature for 0.5h and the resulting suspension filtered through kieselguhr and the filtrate acidified with concentrated hydrochloric acid to give 1-methyl-3-phenylpyrazolo[3,4-b]pyrazine-5,6(4H,7H)-dione (59) (0.35 g; 72%) which formed cream crystals m.p. 339-340° (decomp.) (from glacial acetic acid), ν_{\max} 3300-2500 br (NH) and 1695 br (CO) cm^{-1} .

Found: C, 59.0; H, 4.1; N, 22.2%; M^+ , 242.

$\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}_2$ requires: C, 59.5; H, 4.2; N, 23.1%; M , 242.

(c) A solution of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (0.40 g, 0.002 mol) and cyano acetic acid (0.18 g, 0.002 mol) in dry methylene chloride (50.0 ml) was mixed with a solution of dicyclohexylcarbodiimide (0.46 g, 0.0022 mol) in dry methylene chloride (10.0 ml) and the mixture was stirred with exclusion of atmospheric moisture at room temperature for 1h. The resulting suspension was evaporated and the residue treated with aqueous sodium hypochlorite solution (10% available chlorine) (10.0 ml) and filtered to give dicyclohexylurea (0.57 g) m.p. 200-204° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The alkaline filtrate was acidified with concentrated hydrochloric acid to give an intractable brown solid (0.44 g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture, which was not resolved by flash column

chromatography over silica.

(d) A solution of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (1.6 g, 0.008 mol) and cyanoacetic acid (0.75 g, 0.0088 mol) in dry methylene chloride (150 ml) was mixed with a solution of dicyclohexylcarbodiimide (1.84 g, 0.0088 mol) in dry methylene chloride (10.0 ml) and the mixture stirred at room temperature with exclusion of atmospheric moisture for 1h. The resulting suspension was evaporated and the residue treated with a solution of potassium ferricyanide (2.63 g, 0.008 mol) in water (20.0 ml), followed by aqueous 2M sodium hydroxide solution (20.0 ml) and the mixture stirred at room temperature for 1h. The resulting suspension was filtered to give dicyclohexylurea (1.9 g) m.p. 225-229° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous mother liquor was acidified with concentrated hydrochloric acid to give impure 5-cyano-1-methyl-3-phenylpyrazolo[3,4-b]pyrazin-6(7H)-one (58) (1.7 g; 84%) m.p. 245-250° raised to 285-290° (decomp.) (from dimethylformamide-water) m/e 251, identical (m.p., i.r. and mass spectra) to an authentic sample prepared before.

1-Methyl-3-phenylpyrazolo[3,4-b]pyrazin-6(7H)-one-5-carboxylic acid (61)

A solution of 5-cyano-1-methyl-3-phenylpyrazolo[3,4-b]pyrazin-6(7H)-one (58) (0.50 g, 0.002 mol) in 20% w/v aqueous potassium hydroxide (5.0 ml) was heated under reflux for 1h. The resulting suspension was diluted with water (5.0 ml) and acidified with concentrated hydrochloric acid. The insoluble

solid was slurried with saturated aqueous sodium hydrogen carbonate (10.0 ml) and the suspension was filtered to remove inorganic material and the filtrate acidified with aqueous 2M hydrochloric acid to give 1-methyl-3-phenylpyrazolo[3,4-b]-pyrazin-6(7H)-one-5-carboxylic acid (61) (0.50 g; 93%) which formed yellow crystals m.p. 224-225° (from ethanol), ν_{\max} 3580-2550 br (NH/OH) and 1665 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ (54°) 8.36-8.23 (2H, m, ArH), 7.56-7.38 (3H, m, ArH) and 3.98 (3H, s, NCH_3).

Found: C, 57.5; H, 3.7; N, 20.5%, M^+ , 270.

$\text{C}_{13}\text{H}_{10}\text{N}_4\text{O}_3$ requires: C, 57.8; H, 3.7; N, 20.7%; M, 270.

1-Methyl-3-phenylpyrazolo[3,4-b]pyrazin-6(7H)-one-5-carboxamide (63)

A mixture of 5-cyano-1-methyl-3-phenylpyrazolo[3,4-b]-pyrazin-6(7H)-one (58) (0.50 g, 0.002 mol) and polyphosphoric acid (15.5 g) was stirred mechanically at 120-130° (oil bath) for 10 min. The mixture was diluted with water (15.0 ml) and the precipitated solid was treated with aqueous 2M sodium hydroxide solution to give a yellow solid. This was collected and acidified with aqueous 2M hydrochloric acid to afford 1-methyl-3-phenylpyrazolo[3,4-b]pyrazin-6(7H)-one-5-carboxamide (63) (0.37 g; 69%) which formed yellow crystals m.p. 245-246° (from ethanol-dimethylformamide), ν_{\max} 3460 (NH) and 1670 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.92 (1H, s, NH), 8.58 (1H, s, NH), 8.50-8.39 (2H, m, ArH), 7.52-7.39 (3H, m, ArH), 3.94 (3H, s, NCH_3) and 3.45 (1H, brs, NH).

Found: C, 57.8; H, 4.3; N, 25.5%; M^+ , 269.

$C_{13}H_{11}N_5O_2$ requires: C, 58.0; H, 4.1; N, 26.0%; M , 269.

The Attempted Methylation of 5-Cyano-1-methyl-3-phenylpyrazolo[3,4-b]pyrazin-6(7H)-one (58)

(a) A vigorously stirred suspension of sodium hydride (0.10 g, 0.004 mol) in dry dimethylformamide (2.5 ml) was treated with a solution of 5-cyano-1-methyl-3-phenylpyrazolo[3,4-b]pyrazin-6(7H)-one (58) (0.48 g, 0.002 mol) in dry dimethylformamide (5.0 ml) and the mixture stirred with protection from atmospheric moisture at room temperature for 15 min. The stirred suspension was then treated in one portion with methyl iodide (0.28 g, 0.002 mol) and stirring continued at room temperature for 3h. The mixture was then treated with water (10.0 ml) and extracted with methylene chloride and ethyl acetate to give a three phase system. This was filtered and the solid washed with aqueous 2M hydrochloric acid and combined with a second crop obtained by acidifying the aqueous phase with concentrated hydrochloric acid to give the unreacted pyrazolopyrazinone (58) (total 0.40 g; 83%) m.p. 312-314°, identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the ethyl acetate-methylene chloride extract gave no further identifiable material.

(b) A suspension of 5-cyano-1-methyl-3-phenylpyrazolo[3,4-b]pyrazin-6(7H)-one (58) (0.50 g, 0.002 mol) in 10% w/v aqueous sodium hydroxide (15.0 ml) was treated dropwise with dimethyl sulphate (1.4 ml) and the mixture shaken mechanically at room temperature for 3h, then left stoppered at room

temperature for 18h. The resulting suspension was filtered and the brown solid was washed with aqueous 2M hydrochloric acid (5.0 ml) and combined with a second crop obtained by acidifying the aqueous mother liquor with concentrated hydrochloric acid to give the unreacted pyrazolopyrazinone (58) (0.44 g; 88%) m.p. 302-306° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Oxidation of 5-Cyano-1-methyl-3-phenylpyrazolo-[3,4-b]pyrazin-6(7H)-one (58)

A solution of 5-cyano-1-methyl-3-phenylpyrazolo[3,4-b]-pyrazin-6(7H)-one (58) (0.50 g, 0.002 mol) in glacial acetic acid (20.0 ml) was treated with 30% aqueous hydrogen peroxide solution (2.5 ml) and the suspension was stirred at 50° (oil bath) for 18h. The mixture was hot filtered to give the unreacted pyrazolopyrazinone (58) (0.40 g; 80%) m.p. 315-319° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

Careful evaporation of the aqueous mother liquor gave no further identifiable material.

1,3-Dimethyl-4-nitroso-5-phenylacetamidopyrazole (69)

A solution of phenylacetic acid (1.40 g, 0.01 mol) in dry methylene chloride (10.0 ml) was mixed with a solution of dicyclohexylcarbodiimide (2.3 g, 0.011 mol) in dry methylene chloride (5.0 ml) and the mixture was stirred at room temperature with exclusion of atmospheric moisture, then treated with a solution of 5-amino-1,3-dimethyl-4-nitrosopyrazole (46)

(1.4 g, 0.01 mol) in dry methylene chloride (100 ml) and stirring continued at room temperature for 3h. The resulting suspension was filtered to give a colourless solid which was combined with a second crop obtained by evaporating the filtrate and treating the residue with aqueous 2M sodium hydroxide (20.0 ml) to give dicyclohexylurea (2.6 g) m.p. 223-225°, identical (m.p. and i.r. spectrum) to an authentic sample.

The basic aqueous mother liquor was acidified with concentrated hydrochloric acid to give 1,3-dimethyl-4-nitroso-5-phenylacetamidopyrazole (69) (2.0 g; 78%) which formed green crystals m.p. 119-120° (from toluene), ν_{\max} 3200 br (NH) and 1690 (CO) cm^{-1} , $\delta(\text{CDCl}_3)$ 9.27 (1H, brs, NH), 8.44-8.36 (5H, m, ArH), 3.78 (2H, s, CH_2), 3.68 (3H, s, NCH_3) and 2.70 (3H, s, CH_3).

Found: M^+ , 258.1114

$\text{C}_{13}\text{H}_{14}\text{N}_4\text{O}_2$ requires: M, 258.1117

1,3-Dimethyl-5-phenylpyrazolo[3,4-b]pyrazin-6(7H)-one (72)

A solution of 1,3-dimethyl-4-nitroso-5-phenylacetamidopyrazole (69) (0.51 g, 0.002 mol) in absolute ethanol (10.0 ml) was treated with a solution of sodium (0.18 g, 0.008 g. atom) in absolute ethanol (5.0 ml) and the mixture heated under reflux for 0.5h. The mixture was evaporated and the residue treated with water (5.0 ml) and extracted with methylene chloride (3x25.0 ml) to give an intractable red-brown gum (0.26 g).

The aqueous mother liquor was acidified with concentrated hydrochloric acid and extracted with methylene chloride (3x25.0 ml) to give a brown gum which was triturated with ethanol-light

petroleum to afford 1,3-dimethyl-5-phenylpyrazolo[3,4-b]-pyrazin-6(7H)-one (72) (0.06 g; 12%) which formed yellow needles m.p. 271-273° (from ethyl acetate-ethanol), ν_{\max} 3200-2550 br (NH) and 1640 (CO) cm^{-1} .

Found: M^+ , 240.1024.

$C_{13}H_{12}N_4O$ requires: M , 240.1011.

1-Methyl-4-nitroso-3-phenyl-5-phenylacetamidopyrazole (73)

A solution of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (0.40 g, 0.002 mol) and phenylacetic acid (0.28 g, 0.002 mol) in dry methylene chloride (100 ml) was mixed with a solution of dicyclohexylcarbodiimide (0.45 g, 0.0022 mol) in dry methylene chloride (5.0 ml) and the mixture was stirred with protection from atmospheric moisture at room temperature for 5h. The resulting suspension was filtered and the solid was combined with a second crop obtained by treating the evaporated filtrate with aqueous 2M sodium hydroxide (10.0 ml) to give dicyclohexylurea (0.52 g), m.p. 220-224°, identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous filtrate was acidified with concentrated hydrochloric acid and extracted with methylene chloride (4x50.0 ml) to afford 1-methyl-4-nitroso-3-phenyl-5-phenylacetamidopyrazole (73) (0.17 g; 26%) which formed green crystals m.p. 145-146° (from ethanol), ν_{\max} 3200 (NH) and 1710 (CO) cm^{-1} , $\delta(\text{CDCl}_3)$ 9.38 (1H, brs, NH), 8.32-8.20 (2H, m, ArH), 7.50-7.32 (8H, m, ArH) and 3.78 (5H, s, NCH_3 and CH_2).

Found: C, 67.5; H, 5.0; N, 17.2%; M^+ , 320.

$C_{18}H_{16}N_4O_2$ requires: C, 67.5; H, 5.0; N, 17.5%; M , 320.

The ethanolic filtrate was evaporated to give a green-brown solid (0.24 g) whose t.l.c. in toluene over silica showed it to be a multicomponent mixture, which was not further investigated.

The Reaction of 5-Amino-1-methyl-4-nitroso-3-phenylpyrazole (50) with Phenylacetyl Chloride in the Presence of Triethylamine

A solution of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (0.40 g, 0.002 mol) in dry dioxane (25.0 ml) was stirred at room temperature and treated dropwise with triethylamine (0.23 g, 0.0022 mol), then, cooling the mixture in an ice bath, with a solution of phenylacetyl chloride (0.34 g, 0.0022 mol) in dry dioxane (5.0 ml). The reaction mixture was stirred at room temperature for 2h, then filtered and the solid obtained washed with water (10.0 ml) to give the unreacted amino-nitrosopyrazole (50) (0.022 g; 6%) m.p. 208-212° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The dioxane mother liquor was evaporated and the residue triturated with ether to give a green solid which was heated under reflux in ethanol and hot filtered to give 3,5-diphenyl-1-methylpyrazolo[3,4-b]pyrazin-6(7H)-one (76) (0.04 g; 7%) m.p. 317-321°, ν_{\max} 3120-2500 br (NH) and 1645 (CO) cm^{-1} .

Found: M^+ , 302.1183.

$C_{18}H_{14}N_4O$ requires: M , 302.1168.

Filtration of the cooled ethanolic filtrate gave 1-methyl-

4-nitroso-3-phenyl-5-phenylacetamidopyrazole (73) (0.13 g; 20%) m.p. 132-135° identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the ethanol and ether mother liquors gave intractable gums (total 0.49 g) whose t.l.c. in ethyl acetate over silica showed them to be complex mixtures, which were not further investigated.

The Attempted Oxidation of 5-Amino-1-methyl-4-nitroso-3-phenylpyrazole (50)

(a) Solutions of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (4.0 g, 0.02 mol) in methanol (250 ml) and potassium hydroxide (3.4 g, 0.06 mol) in methanol (150 ml) were mixed and the mixture was treated dropwise while stirring at 0° (ice-salt bath) with an aqueous sodium hypochlorite solution (10% available chlorine) (290 ml), then stirred at 0° for 0.5h. The resulting suspension was filtered and the solid was stirred in water (100 ml) at room temperature for 2h and then recollected to give 1-methyl-3-phenylpyrazolo-[3,4-d]furazan (80) (3.9 g; 96%) which was purified by Kugelrohr distillation under reduced pressure (oil-pump) to give yellow cubes m.p. 109-110°, ν_{\max} 1630 (C=N) cm^{-1} , $\delta(\text{CDCl}_3)$ 8.12-7.99 (2H, m, ArH), 7.52-7.39 (3H, m, Ar) and 3.96 (3H, s, NCH_3).

Found: M^+ , 200.0703.

$\text{C}_{10}\text{H}_8\text{N}_4\text{O}$ requires: M, 200.0698.

(b) A solution of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (0.40 g, 0.002 mol) in dry 1,2-dimethyloxyethane

(40.0 ml) was treated with activated manganese dioxide (3.0 g) and the suspension vigorously stirred at room temperature for 17h. The mixture was filtered through kieselguhr and the filtrate was evaporated to give the unreacted amino-nitrosopyrazole (50) (0.37 g; 93%) m.p. 205-210°, identical (m.p. and i.r. spectrum) to an authentic sample.

The Reduction of 1-Methyl-3-phenylpyrazolo[3,4-d]furan (80)

A solution of 1-methyl-3-phenylpyrazolo[3,4-d]furan (80) (0.40 g, 0.002 mol) in absolute ethanol (50.0 ml) was hydrogenated over 10% palladium-on-charcoal (0.04 g) at room temperature and atmospheric pressure for 3h. Hydrogen was absorbed and the mixture was filtered through kieselguhr and evaporated to give 4,5-diamino-1-methyl-3-phenylpyrazole (85) (yield quantitative) m.p. 112-116° (lit.,¹⁰² 177-178°) identical (m.p. and i.r. spectrum) to an authentic sample prepared later.

4,5-Diamino-1-methyl-3-phenylpyrazole (85)

A solution of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (0.40 g, 0.002 mol) in absolute ethanol (150 ml) was hydrogenated over 10% palladium-on-charcoal (0.04 g) at room temperature and atmospheric pressure for 3h. Hydrogen was absorbed and the mixture was filtered through kieselguhr and evaporated to give a green glass which was triturated with ethyl acetate to afford 4,5-diamino-1-methyl-3-phenylpyrazole (85) (0.28 g; 74%) which formed brown needles m.p. 125-126° (from toluene) (lit.,¹⁰² 177-178°), ν_{\max} 3360, 3300, 3250 and

3190 (NH_2) and 1650 ($\text{C}=\text{N}$) cm^{-1} , $\delta(\text{CDCl}_3)$ 7.75-7.62 (2H, m, ArH), 7.46-7.22 (3H, m, ArH), 3.61 (3H, s, NCH_3) and 2.90 (4H, brs, NH_2).

Found: M^+ , 188.1075.

Calc. for $\text{C}_{10}\text{H}_{12}\text{N}_4$: M , 188.1062.

The ethyl acetate filtrate was evaporated to give an oil (0.034 g) whose t.l.c. in ether over silica showed it to be a complex mixture which was not further investigated.

The Attempted Reaction of 5-Amino-1-methyl-4-nitroso-3-phenylpyrazole (50) with Cyanamide

A solution of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (0.40 g, 0.002 mol) in dry dioxane (25.0 ml) was treated with cyanamide (0.95 g, 0.0022 mol) and the mixture was stirred at room temperature for 4h, then heated under reflux for 5h. The resulting solution was evaporated and the residue treated with water (10.0 ml) and the solid collected to give the unreacted aminino-nitrosopyrazole (50) (0.38 g; 95%) m.p. 215-218° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Reaction of 5-Amino-1-methyl-4-nitroso-3-phenylpyrazole (50) with Urea

5-Amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (0.40 g, 0.002 mol) and urea (0.13 g, 0.022 mol) were intimately mixed and heated at 190-210° (Woods metal bath) for 1h. The dark mixture was treated with water (5.0 ml) and the insoluble solid was collected and extracted with boiling light petroleum

to leave an insoluble dark intractable solid (0.21 g), m.p. 115-120° which defied characterisation.

Evaporation of the light petroleum mother liquor afforded a brown gum (0.14 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex multicomponent mixture, which was not further investigated.

The Attempted Reaction of 5-Amino-1-methyl-4-nitroso-3-phenylpyrazole (50) with Phenyl Isocyanate

A solution of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (0.40 g, 0.002 mol) in dry 1,2-dimethoxyethane (20.0 ml) was mixed with a solution of phenyl isocyanate (0.26 g, 0.0022 mol) in dry 1,2-dimethoxyethane (5.0 ml) and the mixture heated under reflux for 21h. The mixture was evaporated to give a red gum which was triturated with toluene to afford a red-brown solid (0.44 g), whose t.l.c. in ether over silica showed it to be a multicomponent mixture from which no identifiable material could be obtained.

Evaporation of the toluene mother liquor gave a red gum (0.2 g) whose t.l.c. in ether over silica showed it to be a complex mixture, which was not further investigated.

1-Methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103)

(a) A solution of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (2.0 g, 0.01 mol) in dry 1,2-dimethoxyethane (75.0 ml) was heated under reflux with methyl isocyanate (6.8 g, 0.12 mol) added in three equal portions, the second and

third after reaction times of 4h and 8h respectively. The mixture was heated under reflux for a total of 25h then evaporated and the residue triturated with ethyl acetate to give 1-methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) (1.18 g; 52%) which formed red crystals m.p. 179-181° (from toluene), ν_{\max} 1790 (CO) and 1635 (C=N) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.15-8.10 (2H, m, ArH), 7.53-7.49 (3H, m, ArH) and 3.78 (3H, s, NCH_3).

Found: C, 58.1; H, 3.5; N, 24.3%; M^+ , 228.

$\text{C}_{11}\text{H}_8\text{N}_4\text{O}_2$ requires: C, 57.9; H, 3.5; N, 24.6%; M, 228.

The ethyl acetate filtrate was evaporated to give a dark oil (1.54 g) which was subjected to column chromatography over silica.

Elution with toluene-methylene chloride (7:3) afforded a brown gum which was triturated with toluene-light petroleum to give impure unreacted amino-nitrosopyrazole (50) (0.17 g; 9%) identical (i.r. spectrum) to an authentic sample.

(b) A solution of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (0.40 g, 0.002 mol) in dry 1,2-dimethoxyethane (27.0 ml) was treated with methyl isocyanate (0.12 g, 0.002 mol) and the mixture was left stoppered at room temperature for 18h. Evaporation of the mixture afforded the unreacted amino-nitrosopyrazole (50) (yield quantitative) m.p. 218-220°, identical (m.p. and i.r. spectrum) to an authentic sample.

(c) A solution of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (0.40 g, 0.002 mol) in dry 1,2-dimethoxyethane (25.0 ml) was treated with methyl isocyanate (0.12 g, 0.002 mol) and the mixture was heated under reflux for 16.5h.

The mixture was evaporated to give a red solid (0.48 g) whose t.l.c. in ethyl acetate over silica and mass spectrum showed it to be a mixture of the pyrazolooxadiazinone (103) and the unreacted amino-nitrosopyrazole (50) which was not further investigated.

(d) A solution of 5-amino-1-methyl-3-phenylpyrazole (50) (10.1 g, 0.05 mol) and toluene-p-sulphonyl isocyanate (10.86 g, 0.055 mol) in dry 1,2-dimethoxyethane (150 ml) was heated under reflux for 3h, then treated with a further portion of toluene-p-sulphonyl isocyanate (5.0 g, 0.025 mol) and heating under reflux continued for a further 1h. The mixture was evaporated and the residue triturated with ether to give a red solid which was washed with a little toluene to afford 1-methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiaz-6-one (103) (9.2 g; 80%) m.p. 178-179°, identical (m.p. and i.r. spectrum) to an authentic sample prepared in (a) before.

Evaporation of the toluene-ether mother liquor gave a dark brown gum (19.3 g) whose t.l.c. in ether over silica showed it to be a complex mixture, which was not further investigated.

The Reaction of 1-Methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) with Potassium Hydroxide in Aqueous Ethanol

A solution of 1-methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) (0.23 g, 0.001 mol) in ethanol (5.0 ml) was treated with 20% w/v aqueous potassium hydroxide solution (2.5 ml) and the mixture was heated under reflux for

1h. The mixture was evaporated and the residue treated with water (5.0 ml), acidified with concentrated hydrochloric acid and extracted with methylene chloride (3x25.0 ml) to give 1-methyl-4-oximino-3-phenyl- Δ^2 -pyrazolin-5-one (106) (0.19 g; 93%) which formed orange-brown needles m.p. 165-166° (decomp.) (from toluene) (lit.,¹²⁷ 162°), ν_{\max} 3200-2550 br (OH) and 1690 br (CO) cm^{-1} .

Found: C, 59.4; H, 4.5; N, 21.2%; M^+ , 203.

Calc. for $\text{C}_{10}\text{H}_9\text{N}_3\text{O}_2$: C, 59.1; H, 4.5; N, 20.7%; M , 203.

The aqueous acidic mother liquor was neutralised with solid sodium acetate and extracted with methylene chloride (3x25.0 ml) to give 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (0.005 g; 2%) m.p. 216-219° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Reaction of 5-Amino-1-methyl-4-nitroso-3-phenylpyrazole (50) with Potassium Hydroxide in Aqueous Ethanol

A solution of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (0.40 g; 0.002 mol) in ethanol (10.0 ml) was treated with 20% w/v aqueous potassium hydroxide (5.0 ml) and the mixture was heated under reflux for 1h. The mixture was evaporated and the residue treated with water (5.0 ml), acidified with concentrated hydrochloric acid and extracted with methylene chloride to give an orange solid. This was treated with aqueous 2M sodium hydroxide solution, filtered to remove some insoluble material, and the filtrate acidified with concentrated hydrochloric acid and extracted with methylene chloride to yield the unreacted amino-nitrosopyrazole (50) (0.38 g; 95%),

m.p. 212-215° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Reduction of 1-Methyl-3-phenyl-1H,6H-pyrazolo-[4,3-c]-1,2,5-oxadiazin-6-one (103)

(a) A solution of 1-methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) (0.23 g, 0.001 mol) in absolute ethanol (100 ml) was hydrogenated over 10% palladium-on-charcoal (0.03 g) at room temperature and atmospheric pressure for 6h. Hydrogen was absorbed and the resulting mixture was filtered through kieselguhr and the filtrate evaporated to give a glassy green gum (0.25 g) whose t.l.c. in ether over silica showed it to be a multicomponent mixture, which was not further investigated.

(b) A solution of 1-methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) (0.45 g, 0.002 mol) in methanol (50.0 ml) was stirred and treated dropwise over 15 min at room temperature with a solution of sodium borohydride (0.33 g, 0.0088 mol) in water (5.0 ml) and the mixture was stirred at room temperature for 3h. The resulting green solution was evaporated and the residue treated with water and extracted with methylene chloride (4x25.0 ml) to give a red glass (0.25 g) whose t.l.c. in toluene over silica showed it to be a complex multicomponent mixture, which was not further investigated.

The aqueous mother liquor was acidified with concentrated hydrochloric acid and extracted with methylene chloride (3x25.0 ml) to give a brown gum (0.055 g) whose t.l.c. in toluene over silica showed it to be a complex mixture, which was not further investigated.

The Attempted Reaction of 5-Amino-1-methyl-4-nitroso-3-phenylpyrazole (50) with Ethyl Chloroformate

(a) A solution of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (0.40 g, 0.002 mol) in dry dioxane (25.0 ml) was stirred at 0-10° (ice-bath) and treated in one portion with triethylamine (0.23 g, 0.0022 mol) followed dropwise over 5 min with a solution of ethyl chloroformate (0.24 g, 0.0022 mol) in dry dioxane (5.0 ml). The mixture was stirred at room temperature for 2h and the resulting suspension was filtered to remove triethylamine hydrochloride (0.3 g). The filtrate was evaporated to give a red oil (0.74 g) whose t.l.c. in toluene over silica showed it to be a multicomponent mixture which was not further investigated.

(b) A vigorously stirred suspension of sodium hydride (0.06 g, 0.0022 mol) in dry dimethylformamide (2.0 ml) was treated with a solution of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (0.40 g, 0.002 mol) in dry dimethylformamide (4.0 ml) and the mixture was stirred with protection from atmospheric moisture at room temperature for 1h. A solution of ethyl chloroformate (0.24 g, 0.0022 mol) in dry dimethylformamide (2.0 ml) was then added dropwise and the resulting mixture stirred for a further 18h at room temperature. This was followed by dilution with water (10.0 ml) and extraction with methylene chloride (5x50.0 ml) to give a gum (0.47 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex multicomponent mixture, which was not further investigated.

The aqueous alkaline mother liquor was acidified with concentrated hydrochloric acid and extracted with ethyl acetate

to afford a gum (0.055 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture, which was not further investigated.

The Attempted Reaction of 5-Amino-1,3-dimethyl-4-nitrosopyrazole (46) with Methyl Isocyanate

A solution of 5-amino-1,3-dimethyl-4-nitrosopyrazole (46) (0.25 g, 0.002 mol) in dry 1,2-dimethoxyethane (5.0 ml) was treated with methyl isocyanate (0.46 g, 0.008 mol) and the mixture was heated under reflux for 19h. The resulting solution was evaporated to give a brown gum (0.72 g) whose t.l.c. in methylene chloride over silica showed it to be a multi-component mixture, which was not further investigated.

The Attempted Reaction of 5-Amino-1,3-dimethyl-4-nitrosopyrazole (46) with Toluene-p-sulphonyl Isocyanate

A solution of 5-amino-1,3-dimethyl-4-nitrosopyrazole (46) (0.28 g, 0.002 mol) in dry 1,2-dimethoxyethane (20.0 ml) was mixed with a solution of toluene-p-sulphonyl isocyanate (0.4 g, 0.002 mol) in dry 1,2-dimethoxyethane (5.0 ml) and the mixture was stirred at room temperature for 4h, then heated under reflux for 19h. Evaporation of the mixture gave a red gum (0.64 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture, which was not further investigated.

3-Methyl-1-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (119a)

A solution of 5-amino-3-methyl-4-nitroso-1-phenylpyrazole

(117a) (0.81 g, 0.004 mol) and toluene-*p*-sulphonyl isocyanate (0.87 g, 0.0044 mol) in dry 1,2-dimethoxyethane (20.0 ml) was heated under reflux for 1h and then treated with a further portion of toluene-*p*-sulphonyl isocyanate (0.39 g, 0.002 mol) and heating under reflux continued for a further 1h. The mixture was evaporated and triturated with ether to give a red solid which was crystallised from ethanol to give 3-methyl-1-phenyl-1H,6H-pyrazolo[4,3-*c*]-1,2,5-oxadiazin-6-one (119a) (0.14g; 16%) which formed orange needles m.p. 155-156° (from ethanol) (lit.,¹²⁸ 160-162), ν_{\max} 1780 (CO) and 1640 (C=N) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 7.99-7.93 (2H, m, ArH), 7.64-7.35 (3H, m, ArH) and 2.51 (3H, s, CH_3).

Found: C, 57.6; H, 3.7; N, 24.5%; M^+ , 228.

Calc. for $\text{C}_{11}\text{H}_8\text{N}_4\text{O}_2$: C, 57.9; H, 3.5; N, 24.6%; M, 228.

The combined ethereal and ethanolic mother liquors were evaporated to give a gum (2.2 g) which was flash-chromatographed over silica.

Elution with cyclohexane-methylene chloride (3:1) gave impure 3-methyl-1-phenyl-1H,6H-pyrazolo[4,3-*c*]-1,2,5-oxadiazin-6-one (119a) (0.20 g, 21%) identical (i.r. spectrum) to an authentic sample obtained above.

Elution with methylene chloride afforded a green gum tentatively identified as 5-ethoxycarbonylamino-3-methyl-4-nitroso-1-phenylpyrazole (120) (0.38 g; 35%), ν_{\max} 3360w and 3260w (NH) and 1740 br (CO) cm^{-1} , $\delta(\text{CDCl}_3)$ 8.90 (1H, brs, NH), 7.52-7.43 (5H, m, ArH), 3.92 (2H, q, J7Hz, CH_2CH_3), 2.73 (3H, s, CH_3) and 1.07 (3H, t, J7Hz, CH_2CH_3).

Found: M^+ , 274.1065

$C_{13}H_{14}N_4O_3$ requires: M , 274.1066

Further elution with ethyl acetate and ethanol afforded a series of intractable mixtures (total 1.1 g) which were not further investigated.

1,3-Diphenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (119b)

A solution of 5-amino-1,3-diphenyl-4-nitrosopyrazole (117b) (0.53 g, 0.002 mol) and toluene-p-sulphonyl isocyanate (0.40 g, 0.002 mol) in dry 1,2-dimethoxyethane (25.0 ml) was heated under reflux for 1h followed by addition of a second portion of toluene-p-sulphonyl isocyanate (0.20 g, 0.001 mol) and heating under reflux continued for a further 1h. The resulting solution was evaporated to give a red gum which was triturated with ethyl acetate to afford 1,3-diphenyl-1H,6H-pyrazolo-[4,3-c]-1,2,5-oxadiazin-6-one (119b) (0.44 g; 76%) as red needles m.p. 185-187° (decomp.) (from ethanol-dimethylformamide), ν_{\max} 1765 (CO) and 1630 (C=N) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.26-8.02 (4H, m, ArH) and 7.76-7.43 (6H, m, ArH).

Found: C, 66.1; H, 3.4; N, 19.2%; M^+ , 290.

$C_{16}H_{10}N_4O_2$ requires: C, 66.2; H, 3.5; N, 19.3%; M , 290.

The ethyl acetate filtrate was evaporated to give a red gum (0.78 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture, which was not further investigated.

The Attempted Reaction of 5-Amino-1-methyl-4-nitroso-3-phenylpyrazole (50) with Phenyl Isothiocyanate

(a) A solution of 5-amino-1-methyl-4-nitroso-3-phenyl-

pyrazole (50) (0.40 g, 0.002 mol) in dry 1,2-dimethoxyethane (20.0 ml) was mixed with a solution of phenyl isothiocyanate (0.28 g, 0.002 mol) in dry 1,2-dimethoxyethane (5.0 ml) and the mixture was heated under reflux for 21h. Evaporation of the mixture afforded a gummy solid which was triturated with ether-light petroleum to give the unreacted amino-nitroso-pyrazole (50) (yield quantitative) m.p. 208-212°, identical (m.p. and i.r. spectrum) to an authentic sample.

(b) A solution of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (0.40 g, 0.002 mol) in dry dimethylformamide (5.0 ml) was mixed with a solution of phenyl isothiocyanate (0.27 g, 0.002 mol) in dry dimethylformamide (5.0 ml) and the mixture was heated under reflux for 25h. The resulting solution was evaporated to give a glassy brown gum whose t.l.c. in ether over silica showed it to be a multicomponent mixture, which was not further investigated.

The Attempted Reaction of 5-Amino-1-methyl-4-nitroso-3-phenylpyrazole (50) with Ethoxycarbonyl Isothiocyanate

A solution of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (0.40 g, 0.002 mol) in dry 1,2-dimethoxyethane (25.0 ml) was treated with ethoxycarbonyl isothiocyanate (0.29 g, 0.002 mol) and the mixture was heated under reflux for 9h. The mixture was evaporated and the residue treated with ether to give impure unreacted amino-nitrosopyrazole (50) (0.17 g; 42%) m.p. 185-188°, identical (i.r. spectrum) to an authentic sample.

The ethereal filtrate was evaporated to give a red oil (0.53 g) whose t.l.c. in ether over silica showed it to be a

complex mixture, which was not further investigated.

The Attempted Reaction of 5-Amino-1-methyl-4-nitroso-3-phenylpyrazole (50) with Carbon Disulphide

A solution of 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (0.40 g, 0.002 mol) in methanol (10.0 ml) was heated under reflux and treated dropwise with carbon disulphide (2.0 ml). After heating under reflux for 4h and addition of a second portion of carbon disulphide (2.0 ml) the mixture was heated under reflux for a further 3h. The mixture was evaporated to give the unreacted amino-nitrosopyrazole (50) (0.35 g; 88%) m.p. 208-211°, identical (m.p. and i.r. spectrum) to an authentic sample.

The Reaction of 1-Methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) with Ethanolic Methylamine

1-Methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) (0.23 g, 0.001 mol) was treated with 33% w/v ethanolic methylamine solution (5.0 ml) and the mixture was heated under reflux for 1h. The resulting solution was evaporated and the residue triturated with ether to afford 5-amino-1-methyl-4-nitroso-3-phenylpyrazole (50) (0.093 g; 46%) m.p. 202-206° (from toluene), identical (m.p. and i.r. spectrum) to an authentic sample.

The ether and toluene mother liquors were evaporated to give gums (total 0.1 g) whose t.l.c. in ethyl acetate over silica showed them to be complex multicomponent mixtures, which were not further investigated.

1-Benzyl-3-(1-methyl-4-nitroso-3-phenylpyrazol-5-yl)urea

(130a)

A solution of 1-methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) (0.46 g, 0.002 mol) in dry dioxane (50.0 ml) was treated dropwise with stirring at room temperature with benzylamine (0.25 g, 0.0022 mol) and the mixture was stirred at room temperature for 2h. The resulting solution was evaporated to give 1-benzyl-3-(1-methyl-4-nitroso-3-phenylpyrazol-5-yl)urea (130a) (0.67 g; 100%) which formed green crystals m.p. 177-178° (decomp.) (from toluene), ν_{\max} 3350 and 3300 (NH) and 1670 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 9.54 (1H, br, NH), 8.24-8.12 (2H, m, ArH), 7.82 (1H, t, J6Hz, NHCH_2), 7.60-7.48 (3H, m, ArH), 7.38-7.26 (5H, m, ArH), 4.35 (2H, d, J6Hz, CH_2) and 3.68 (3H, s, NCH_3).

Found: C, 64.3; H, 5.1; N, 20.3%; M^+ , 335.1402.

$\text{C}_{18}\text{H}_{17}\text{N}_5\text{O}_2$ requires: C, 64.5; H, 5.1; N, 20.9%; M , 335.1382.

1,1-Diethyl-3-(1-methyl-4-nitroso-3-phenylpyrazol-5-yl)urea

(130b)

A solution of 1-methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) (0.45 g, 0.002 mol) in dry dioxane (50.0 ml) was treated dropwise with stirring at room temperature with diethylamine (0.58 g, 0.008 mol) and the mixture was stirred at room temperature for 1h. The green solution obtained was evaporated and the residue triturated with ethyl acetate to give a green solid which was combined with a second crop obtained by concentrating the ethyl acetate mother liquor to give 1,1-diethyl-3-(1-methyl-4-nitroso-3-phenylpyrazol-5-yl)urea (130b) (0.41 g; 69%) which formed green crystals

m.p. 78-79° (from light petroleum), ν_{\max} 3200-2500 br (NH) and 1695 (CO) cm^{-1} , $\delta(\text{CDCl}_3)$ 11.0 (1H, br s, NH), 8.37-8.24 (2H, m, ArH), 7.56-7.41 (3H, m, ArH), 3.82 (3H, s, NCH_3), 3.43 (4H, q, J 7.0Hz, CH_2) and 1.34 (6H, t, J 7.0Hz, CH_3).

Found: C, 59.7; H, 6.1; N, 22.6%; M^+ , 301.1558.

$\text{C}_{15}\text{H}_{19}\text{N}_5\text{O}_2$ requires: C, 59.8; H, 6.4; N, 23.2%; M , 301.1539.

1-Benzyl-1-methyl-3-(1-methyl-4-nitroso-3-phenylpyrazol-5-yl)-urea (130c)

A solution of 1-methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) (0.46 g, 0.002 mol) in dry dioxane (50.0 ml) was treated dropwise with stirring at room temperature with N-benzylmethylamine (0.27 g, 0.022 mol) and the mixture was stirred at room temperature for 1h. The resulting solution was evaporated, the residue treated with aqueous 2M hydrochloric acid (10.0 ml) and extracted with methylene chloride to give a dark oil (0.87 g) which was subjected to flash column chromatography over silica.

Elution with methylene chloride afforded a solid which crystallised from toluene-light petroleum to give impure unreacted pyrazolo-oxadiazinone (103) (0.03 g; 6%) m.p. 174-177, identical (i.r. spectrum) to an authentic sample.

Elution with methylene chloride afforded 1-benzyl-1-methyl-3-(1-methyl-4-nitroso-3-phenylpyrazol-5-yl)urea (130c) (0.23 g; 33%) m.p. 93-94°, ν_{\max} 3260 br (NH) and 1690 (CO) cm^{-1} , $\delta(\text{CDCl}_3)$ 10.25 (1H, br s, NH), 8.37-8.25 (2H, m, ArH), 7.51-7.33 (8H, m, ArH), 4.59 (2H, s, CH_2), 3.85 (3H, s, pyrazole NCH_3) and 3.10 (3H, s, NCH_3).

Found: C, 65.4; H, 5.5; N, 19.6%; M^+ , 349.

$C_{19}H_{19}N_3O_2$ requires: C, 65.3; H, 5.5; N, 20.1%; M^+ , 349.

Further elution with ethyl acetate followed by ethanol gave only intractable gums and oils (total 0.3 g) from which no identifiable material could be obtained.

1-[N-(1-Methyl-4-nitroso-3-phenylpyrazol-5-yl)carbamoyl]-pyrrolidine (130d)

A solution of 1-methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) (0.46 g, 0.002 mol) in dry dioxane (50.0 ml) was treated dropwise with stirring at room temperature with pyrrolidine (0.16 g, 0.0022 mol) and the mixture was stirred at room temperature for 1h. The mixture was evaporated to give 1-[N-(1-methyl-4-nitroso-3-phenylpyrazol-5-yl)carbamoyl]pyrrolidine (130d) (0.59 g; 99%) which formed green crystals m.p. 134-135° (from toluene-light petroleum), ν_{\max} 3500-2510 br (NH) and 1690 (CO) cm^{-1} , $\delta(\text{CDCl}_3)$ 11.00 (1H, brs, NH), 8.35-8.22 (2H, m, ArH), 7.52-7.38 (3H, m, ArH), 3.88 (3H, s, NCH_3), 3.52 [4H, brs, $\text{N}(\text{CH}_2)_2$] and 2.04 [4H, brs, $(\text{CH}_2)_2$].

Found: C, 60.5; H, 5.7; N, 22.9%; M^+ , 299.1388.

$C_{15}H_{17}N_5O_2$ requires: C, 60.2; H, 5.7; N, 23.4%; M , 299.1382.

The Attempted Reaction of 1-Methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) with Piperidine

A solution of 1-methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) (0.46 g, 0.002 mol) in dry dioxane (50.0 ml) was treated dropwise with stirring at room temperature with piperidine (0.19 g, 0.0022 mol) and the mixture was

stirred at room temperature for 1h. The resulting solution was evaporated to give a green gum which was treated with aqueous 2M hydrochloric acid (10.0 ml) and extracted with methylene chloride to give a green-brown gum (0.69 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture, which was not further investigated.

4-[N-(1-Methyl-4-nitroso-3-phenylpyrazol-5-yl)carbamoyl]-morpholine (130f)

A solution of 1-methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) (0.46 g, 0.002 mol) in dry dioxane (50.0 ml) was treated dropwise with stirring at room temperature with morpholine (0.19 g, 0.0022 mol) and the mixture was stirred at room temperature for 1h. The mixture was evaporated to give 4-[N-(1-methyl-4-nitroso-3-phenylpyrazol-5-yl)carbamoyl]-morpholine (130f) (0.56 g; 89%) which formed green needles m.p. 163-164° (decomp.) (from toluene), ν_{\max} 3280 (NH) and 1700 (CO) cm^{-1} , $\delta(\text{CDCl}_3)$ 8.35-8.24 (2H, m, ArH), 7.52-7.40 (3H, m, ArH), 3.81 (3H, s, NCH_3) and 3.80-3.53 (8H, m, morpholine CH_2).

Found: C, 57.0; H, 5.4; N, 21.9%; M^+ , 315.

$\text{C}_{15}\text{H}_{17}\text{N}_5\text{O}_3$ requires: C, 57.1; H, 5.4; N, 22.2%; M , 315.

The Attempted Reaction of 1-Methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) with N-Phenacylaniline

A solution of 1-methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) (0.46 g, 0.002 mol) in dry dioxane (50.0 ml) was treated dropwise with stirring with a solution of N-phenacylaniline (0.47 g, 0.0022 mol) in dry dioxane

(50.0 ml) and the mixture was stirred at room temperature for 1h, then heated under reflux for 1h. The resulting solution was evaporated to give a dark glassy solid (0.84 g) whose t.l.c. in ether over silica showed it to be a close-running multicomponent mixture, which was not further investigated.

The Attempted Base-catalysed Cyclisation of 1-Benzyl-3-(1-methyl-4-nitroso-3-phenylpyrazol-5-yl)urea (130a)

A solution of 1-benzyl-3-(1-methyl-4-nitroso-3-phenylpyrazol-5-yl)urea (130a) (0.34 g, 0.001 mol) in aqueous 2M sodium hydroxide (2.5 ml) was heated under reflux for 0.5h. The mixture was acidified with aqueous 2M hydrochloric acid and extracted with methylene chloride (3x25.0 ml) to give a gummy solid. This was triturated with ether to give an orange solid (0.15 g) which was shown by t.l.c. in ether over silica to be a multicomponent mixture from which no identifiable material was obtained.

Evaporation of the ethereal filtrate gave a red glassy solid (0.07 g) whose t.l.c. in ether over silica showed it to be a close-running multicomponent mixture, which was not further investigated.

The Attempted Reductive Cyclisation of 1-[N-(1-Methyl-4-nitroso-3-phenylpyrazol-5-yl)carbamoyl]pyrrolidine (130d)

(a) Using triethyl phosphite as the reducing agent

A solution of 1-[N-(1-methyl-4-nitroso-3-phenylpyrazol-5-yl)carbamoyl]pyrrolidine (130d) (0.30 g, 0.001 mol) in dry toluene (25.0 ml) was treated with triethyl phosphite (0.17 g,

0.001 mol) and the mixture was heated under reflux for 1h. The mixture was evaporated and the residue triturated with ether-light petroleum to give a brown gum (0.4 g) whose t.l.c. in ethyl acetate over silica showed it to be a multi-component mixture from which no identifiable material could be obtained.

(b) Using sodium dithionite as the reducing agent

A solution of 1-[N-(1-methyl-4-nitroso-3-phenylpyrazol-5-yl)carbamoyl]pyrrolidine (130d) (0.30 g, 0.001 mol) in 60% v/v aqueous ethanol (50.0 ml) was treated with sodium dithionite (0.30 g) and the mixture was heated under reflux for 1h. A second portion of sodium dithionite (0.30 g) was added, and heating under reflux continued for a further 1h. The mixture was then evaporated and the residue treated with water (10.0 ml) and extracted with methylene chloride to give a green glassy solid (0.17 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture from which no identifiable material was obtained.

N-(1-Methyl-4-nitroso-3-phenylpyrazol-5-yl)carbamoylhydrazine (147a)

A solution of 1-methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) (1.8 g, 0.008 mol) in dry dioxane (150 ml) was treated with 100% hydrazine monohydrate (0.46 g, 0.0088 mol) and the mixture was stirred at room temperature for 1h. The resulting solution was evaporated to give a green solid tentatively formulated as N-(1-methyl-4-nitroso-3-phenylpyrazol-5-yl)carbamoylhydrazine (147a) (2.0 g; 95%) m.p. 215-225° (decomp.) which decomposed on attempted

purification by crystallisation from various organic solvents, ν_{\max} 3400-2500 br (NH) and 1710 (CO) cm^{-1} .

The Thermal Reaction of N-(1-Methyl-4-nitroso-3-phenylpyrazol-5-yl)carbamoylhydrazine (147a) in Ethanol

A solution of N-(1-methyl-4-nitroso-3-phenylhydrazol-5-yl)carbamoylhydrazine (147a) (0.56 g, 0.002 mol) in ethanol (10.0 ml) was heated under reflux for 1h. The resulting solution was evaporated and the solid obtained subjected to flash column chromatography over silica.

Elution with methylene chloride afforded a yellow solid (0.29 g) whose t.l.c. showed it to be a multicomponent mixture, which was not further investigated.

Elution with methylene chloride-ethyl acetate (1:1) gave intractable yellow solids (total 0.07 g) from which no identifiable material was obtained.

Elution with ethyl acetate afforded a yellow solid tentatively formulated as 3-(2-methylhydrazono-1-oximino-2-phenyl)-ethyl-1H-1,2,4-triazol-5(4H)-one (149a) (0.12 g; 23%) which formed cream crystals m.p. 222-223° (from toluene-ethanol), ν_{\max} 3450-2600 br (NH/OH) and 1730 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 12.15 (1H, s, NH), 11.80 (1H, s, NH), 11.59 (1H, s, OH), 7.40-7.08 (5H, m, ArH), 6.28 (1H, q, J4Hz, NHCH₃) (collapses to a s, δ 6.28 on irradiation at δ 2.91) and 2.91 (3H, d. J4Hz, NHCH₃).

Found: C, 51.1; H, 4.7; N, 27.3%; M^+ , 260.1021.

C₁₁H₁₂N₆O₂ requires: C, 50.8; H, 4.6; N, 26.9%; M, 260.1022.

The Attempted Reaction of 1-Methyl-3-phenyl-1H,6H-pyrazolo-[4,3-c]-1,2,5-oxadiazin-6-one (103) with Phenylhydrazine

A solution of 1-methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) (0.46 g, 0.002 mol) in dry dioxane (50.0 ml) was stirred at room temperature, treated with phenylhydrazine (0.24 g, 0.0022 mol) and stirring continued at room temperature for 2h. The mixture was evaporated and the residue treated with aqueous 2M hydrochloric acid and extracted with methylene chloride to give a brown glassy solid (0.28 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture, which was not further investigated.

1-[N-(1-Methyl-4-nitroso-3-phenylpyrazol-5-yl)carbamoyl]-2-(toluene-p-sulphonyl)hydrazine (147c)

A solution of 1-methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) (0.46 g, 0.002 mol) in dry dioxane (50.0 ml) was treated with toluene-p-sulphonylhydrazine (0.41 g, 0.0022 mol) and the mixture was stirred at room temperature for 4h. The mixture was evaporated and the green solid (0.82 g) obtained subjected to flash column chromatography over silica.

Elution with methylene chloride-ethyl acetate and ethyl acetate afforded 1-[N-(1-methyl-4-nitroso-3-phenylpyrazol-5-yl)carbamoyl]-2-toluene-p-sulphonylhydrazine (147c) (0.63 g; 77%) which formed green crystals m.p. 167-168° (decomp.) (from ethanol-dimethylformamide), ν_{\max} 3270 (NH) and 1730 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 9.76 (2H, brs, NH), 9.27 (1H, brs, NH), 8.16-8.11 (2H, m, ArH), 7.76 (2H, d, J8Hz, ArH), 7.59-7.47 (3H, m, ArH), 7.45 (2H, d, J8Hz, ArH), 3.52 (3H, s, NCH_3), and 2.39 (3H, s, CH_3).

Found: C, 52.0; H, 4.7; N, 20.5%; M^+ , 414.

$C_{18}H_{18}N_6O_4S$ requires: C, 52.2; H, 4.4; N, 20.3%; M , 414.

The Attempted Base-catalysed Cyclisation of 1-[N-(1-Methyl-4-nitroso-3-phenylpyrazol-5-yl)carbamoyl]-2-toluene-p-sulphonylhydrazine (147c)

A solution of 1-[N-(1-methyl-4-nitroso-3-phenylpyrazol-5-yl)carbamoyl]-2-(toluene-p-sulphonyl)hydrazine (147c) (0.31 g, 0.0008 mol) in aqueous 2M sodium hydroxide (5.0 ml) was heated under reflux for 15 min. The resulting yellow solution was acidified with concentrated hydrochloric acid and extracted with methylene chloride (3x25.0 ml) to give an orange-red oil (0.23 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture, which was not further investigated.

5-Acetyl-1,6-dimethyl-3-phenylpyrazolo[3,4-c]pyrazine (152)
or 6-Acetyl-1,5-dimethyl-3-phenylpyrazolo[3,4-c]pyrazine (153)

A solution of 1-methyl-3-phenyl-1H,6H-pyrazolo[4,3-c]-1,2,5-oxadiazin-6-one (103) (0.46 g, 0.002 mol) and acetyl-acetone (0.20 g, 0.002 mol) in dry dioxane (50.0 ml) was treated with triethylamine (0.20 g, 0.002 mol) and the mixture was stirred at room temperature for 2h, then heated under reflux for 2.5h. The mixture was evaporated and the residue triturated with ethanol to give 5-acetyl-1,6-dimethyl-3-phenylpyrazolo[3,4-c]pyrazine (152) or 6-acetyl-1,5-dimethyl-3-phenylpyrazolo[3,4-c]pyrazine (153) (0.14 g; 26%) which formed yellow crystals m.p. 113-115° (from ethanol), ν_{\max} 1690 (CO) cm^{-1} , $\delta(\text{CDCl}_3)$ 8.50-8.39 (2H, m, ArH), 7.52-7.41

(3H, m, ArH), 4.13 (3H, s, NCH₃), 2.94 (3H, s, COCH₃) and 2.82 (3H, s, CH₃).

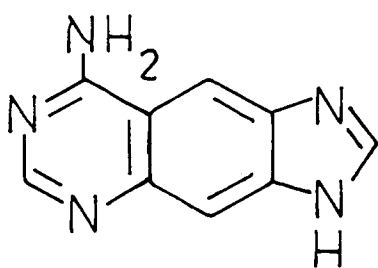
Found: C, 67.0; H, 5.1; N, 21.2%; M⁺, 266.1167.

C₁₅N₁₄N₄O requires: C, 67.7; H, 5.3; N, 21.0%; M, 266.1168.

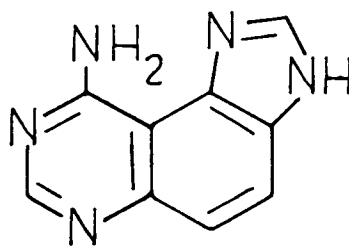
The ethanolic filtrate was evaporated to give a brown gum (0.33 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture, which was not further investigated.

CHAPTER FOUR

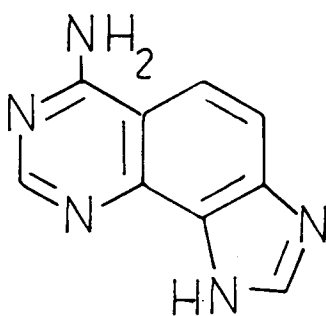
New Synthetic Approaches to N-Oxygenated 'Stretched' Purines, Pteridines and Their Azalogues



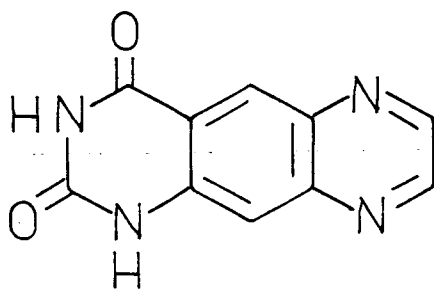
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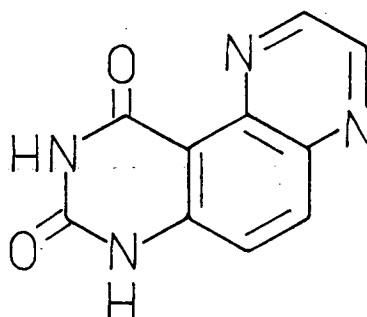
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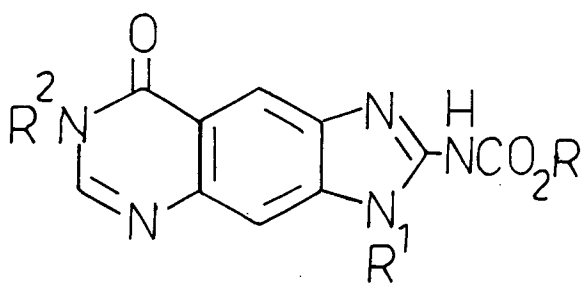
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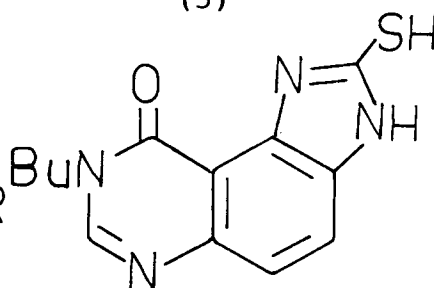
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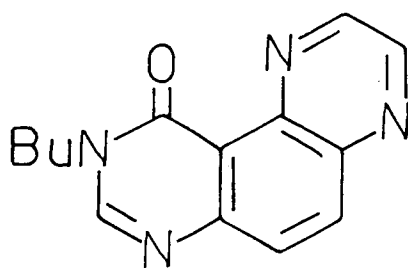
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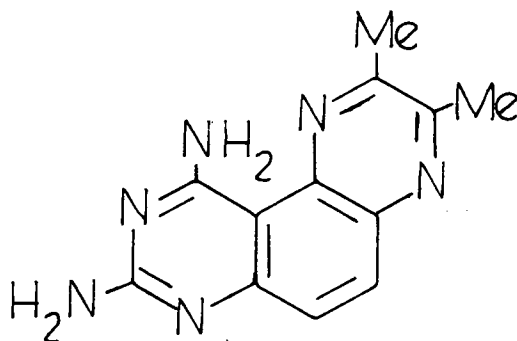
(6)



(7)

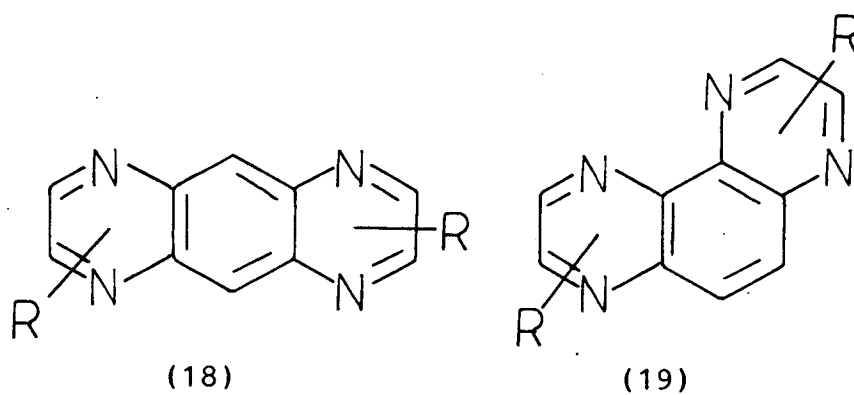
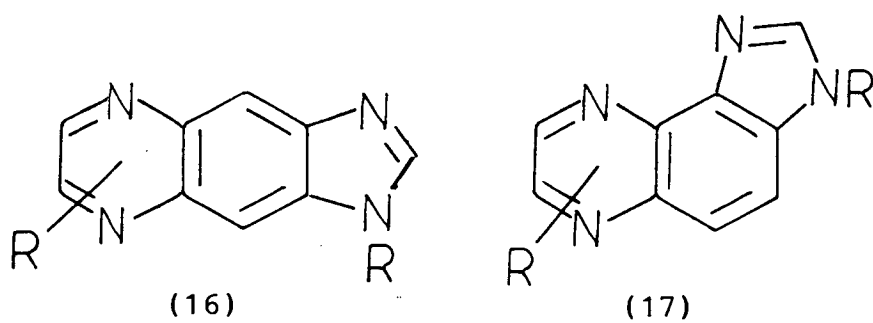
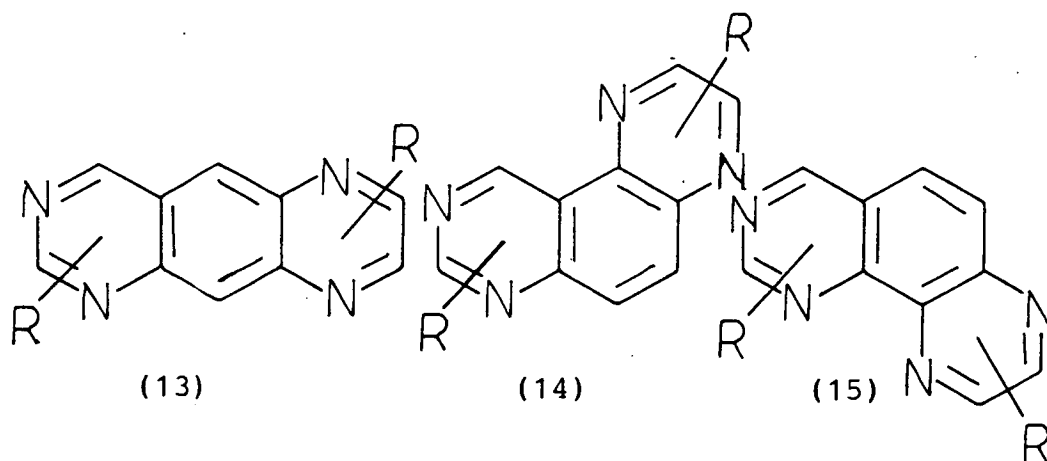
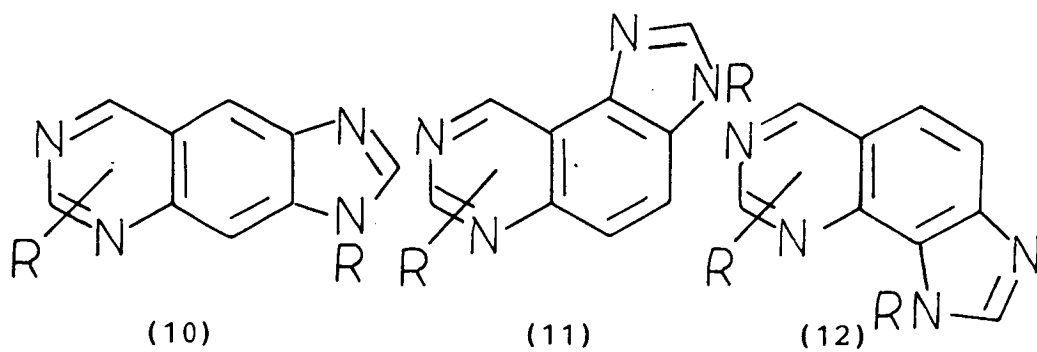


(8)



(9)

Scheme 1

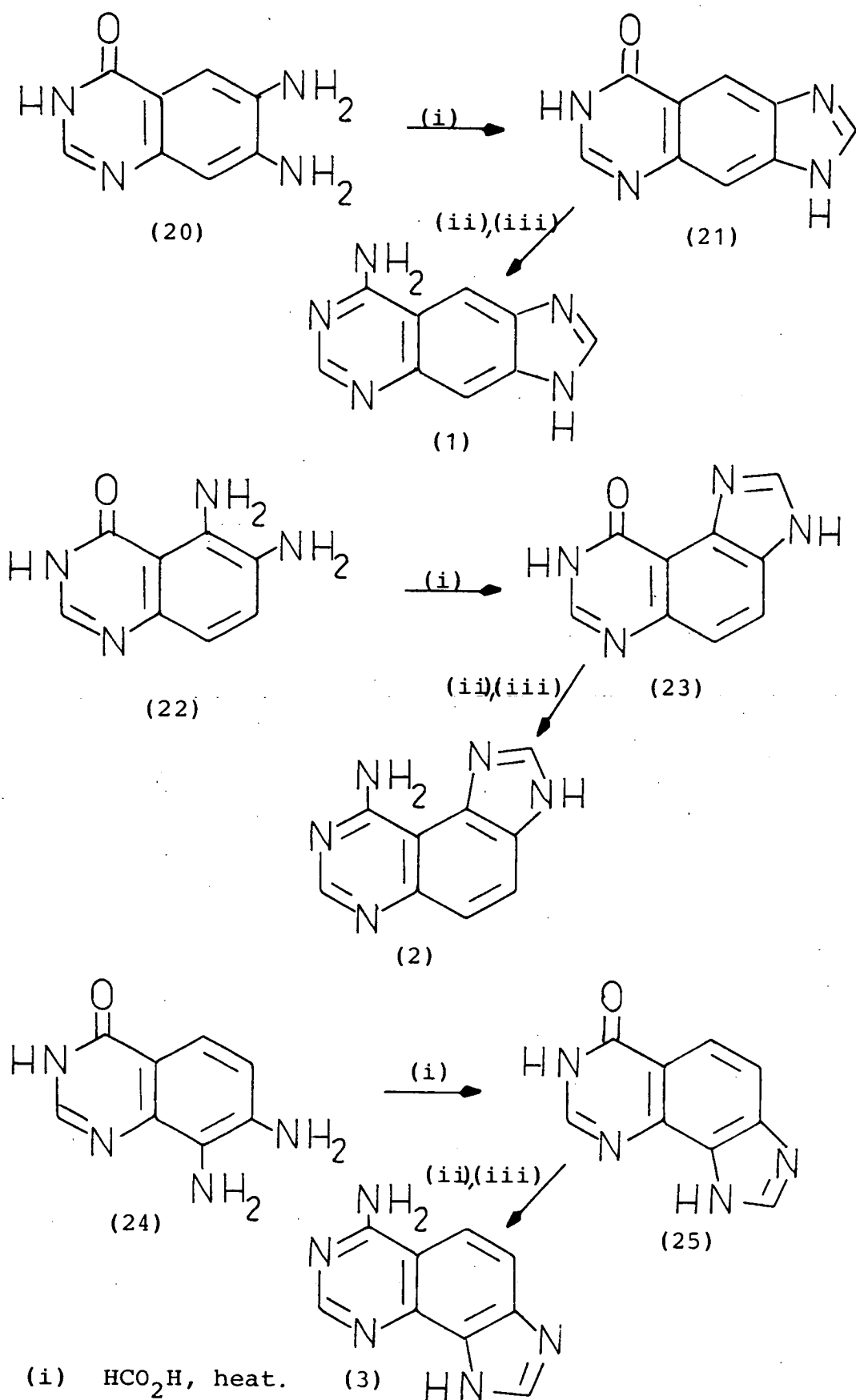


Scheme 2

New Synthetic Approaches to N-Oxygenated 'Stretched' Purines, Pteridines and Their Azalogues

In the past few years considerable interest has been shown in the synthesis of 'stretched-out' analogues of naturally occurring purines and pteridines, such as (Scheme 1) lin-benzoadenine (1),¹⁴⁰ prox-benzoadenine (2),¹⁴¹ dist-benzoadenine (3),¹⁴¹ lin-benzolumazine (4)¹⁴² and prox-benzolumazine (5)¹⁴³ as dimensional probes for enzyme-coenzyme binding sites. Leonard¹⁴⁴ has recently reviewed the synthesis of 'stretched' adenine ribo-nucleotides and describes their ability to both stimulate and inhibit enzyme activity. 'Stretched-out' analogues of purines and pteridines also show other biological properties, Kumar et al.¹⁴⁵ (Scheme 1) have reported 100% clearance of hymenolepis nana by the lin-benzopurine derivative (6) and diuretic, hypoglycemic and weak spasmolytic activity have been reported¹⁴⁶ for prox-benzopurine and benzopteridine derivatives (7) and (8). Johnson et al.¹⁴⁷ have also reported antimicrobial activity for the prox-benzopteridine derivative (9).

However the synthesis of N-oxygenated 'stretched' purines, pteridines and related polyazaheterocyclic systems has not been reported to date and was of considerable interest in view of the utility of such compounds as intermediates in the synthesis of other biologically active 'stretched' purines and pteridines. Moreover N-oxygenated 'stretched' purines and pteridines might possess interesting biological activity in their own right. This chapter describes investigations into the synthesis (Scheme 2) of N-oxygenated derivatives of 'stretched' purines (10)-(12), pteridines (13)-(15), imidazoquinoxalines (16)-(17), and

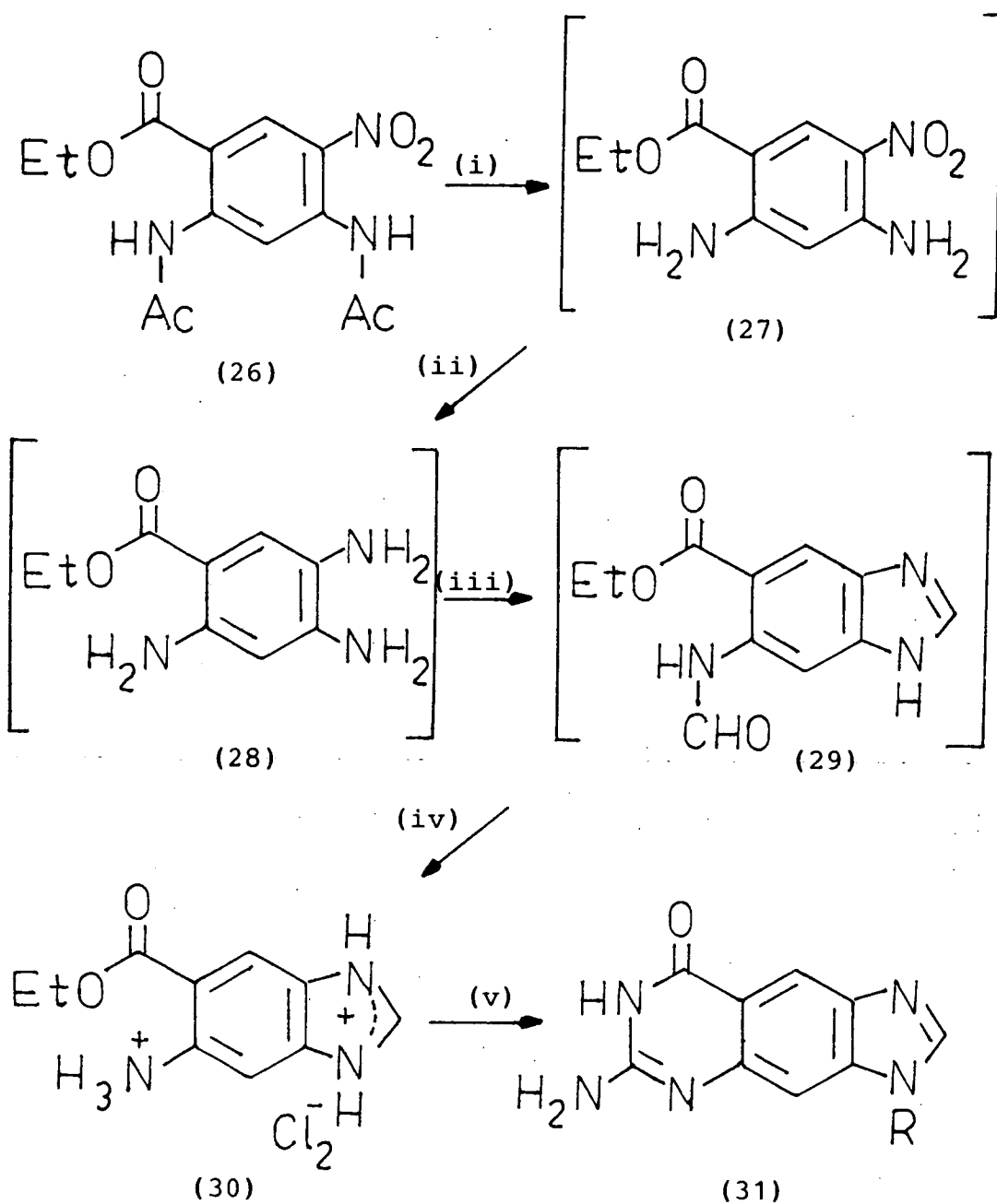


(i) HCO_2H , heat.

(ii) P_2S_5 , pyridine, heat.

(iii) NH_3 -BuOH, 150° - 200° .

Scheme 3



- (i) HCl, EtOH, heat.
(ii) H₂, Pd-C, HCO₂H.
(iii) HCO₂H, heat.
(iv) HCl, EtOH, heat.
(v) HCl, NH₂CN, EtOH.

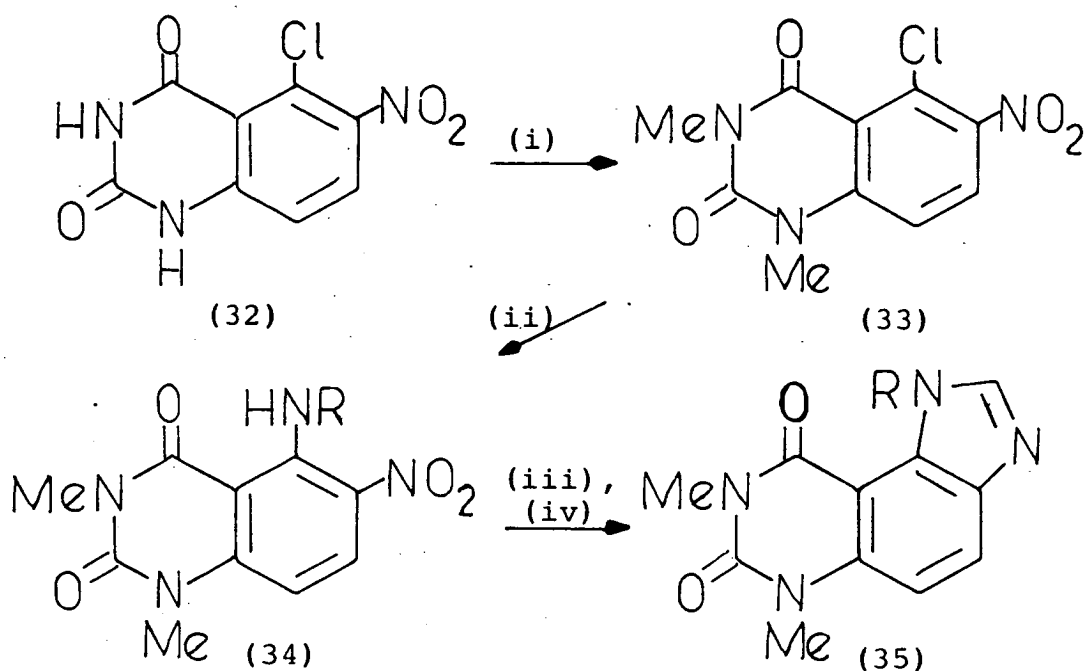
R
a; H
b; β-D-ribofuranose

Scheme 4

pyrazinoquinoxalines (18) and (19). The term 'stretched' is used as a general term for tricyclic ring systems where two heterocyclic rings are separated from each other by a benzene ring, for example (Scheme 2) the 'stretched' purine derivatives (10)-(12). Leonard *et al.*¹⁴⁰ have further subdivided this general term by using the trivial names lin-, prox- and dist-benzopurines for ring systems (10), (11) and (12) respectively, corresponding to the disposition of the heterocyclic rings in the tricyclic ring systems.

The synthesis by Leonard *et al.* (Scheme 3)¹⁴⁰ of lin-benzoadenine (1) involves ring closure of the diaminoquinazolone (20) with formic acid to give the imidazoquinazolone (21) in good yield. Treatment of the latter with phosphorus pentasulphide in pyridine gave the corresponding thio derivative which on heating with ammonia-saturated butanol in a sealed tube gave the observed product, lin-benzoadenine (1). Similarly (Scheme 3)¹⁴¹ treatment of the diaminoquinazolones (22) and (24) with formic acid afforded the imidazoquinazolone derivatives (23) and (25) which on treatment with phosphorus pentasulphide, followed by reaction with ammonia-saturated butanol gave prox- and dist-benzoadenine (2) and (3) respectively.

Leonard and Keyser¹⁴⁸ have prepared (Scheme 4) lin-benzcguanine (31a) from ethyl 2,4-diacetamido-5-nitrobenzoate (26) by a series of reactions without isolation of the intermediates, in high yield. Thus, deprotection of the amino substituent by acid hydrolysis gave the diaminobenzene derivative (27), catalytic hydrogenation over palladium-on-charcoal in formic acid followed by heating under reflux



(i) Me_2SO_4 , Et_3NHOH^+ , 30-35°.

(ii) RNH_2 , BuOH, 140-150°.

(iii) H_2 , Pd-C, HCO_2H .

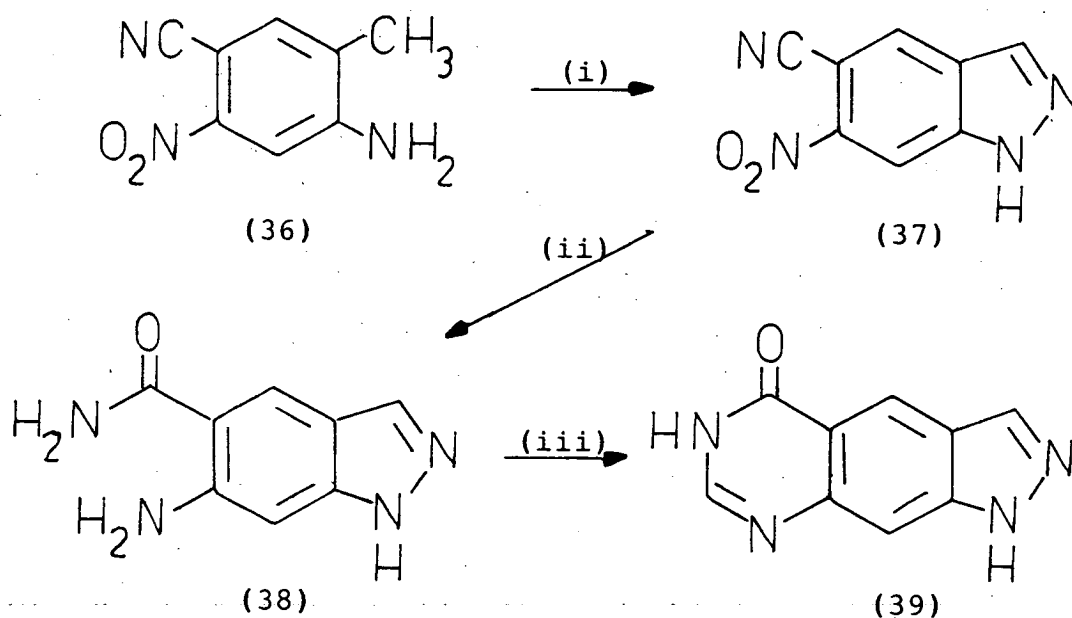
(iv) HCO_2H , heat.

R

a; H

b; Me

Scheme 5



(i) NaNO_2 , H_2O , AcOH.

(ii) NH_2NH_2 , H_2O , EtOH, Raney Nickel, 45°.

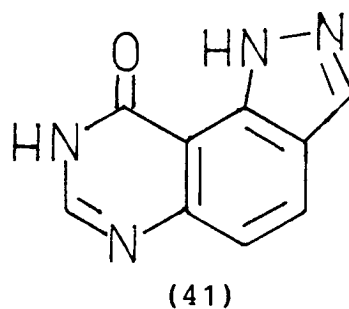
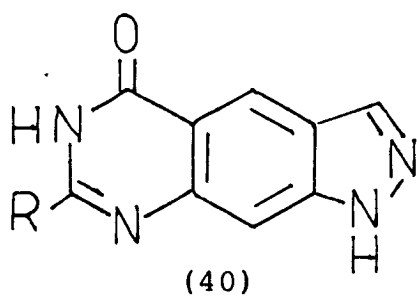
(iii) HCO_2H , H_2O , heat.

Scheme 6

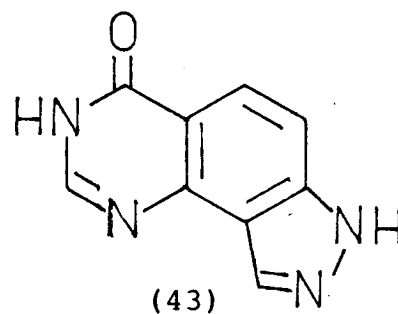
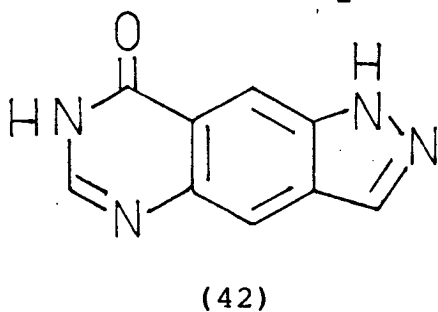
afforded the benzimidazole derivative (29), which proved to be unstable under both air and nitrogen atmospheres. However, heating the benzimidazole derivative (29) in ethanolic HCl gave the dihydrochloride (30) which on heating in a large excess of ethanolic cyanamide afforded lin-benzoguanine (31a). The synthesis of β -D-ribofuranosyl lin-benzoguanine (31b) from ethyl 2,4-diacetamido-5-nitrobenzoate (26) has also been described by Leonard and Keyser.¹⁴⁹

Schneller and Christ¹⁴² synthesised (Scheme 5) prox-benzothiophylline (35a) and prox-benzocaffeine (35b) by methylation of the quinazolinedione derivative (32) to give the dimethyl-quinazolinedione (33). Amination of the latter gave the 5-amino derivative (34a), which on catalytic hydrogenation over palladium-on-charcoal, followed by heating under reflux in formic acid, gave prox-benzothiophylline (35a). Reaction of the dimethyl-quinazolinedione (33) with methylamine gave the 5-methylamino derivative (34b) which afforded prox-benzocaffeine (35b) on catalytic hydrogenation and heating under reflux in formic acid.

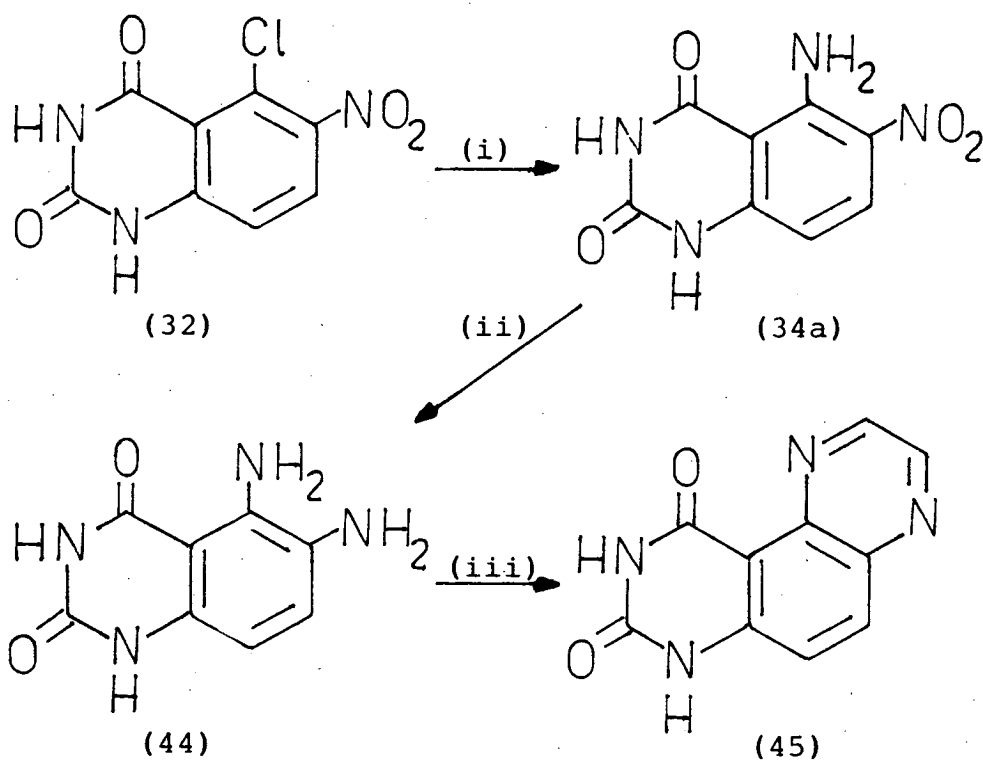
The synthesis (Scheme 6) of lin-benzoallopurinol (39) from 4-amino-5-methyl-2-nitrobenzonitrile (36) has been reported in the literature.¹⁵⁰ Treatment of the amino-benzonitrile (36) with sodium nitrite gave an excellent yield of the nitroindazole derivative (37), reduction and partial hydrolysis of which afforded the indazole-carboxamide (38). Direct cyclisation of the latter with formic acid gave a good yield of lin-benzoallopurinol (39). This compound was of interest because allopurinol is the drug of choice for the treatment of hyperuricemia in man. Cuny, Lichtenthaler and



\underline{R}
 a; OH
 b; NH₂



Scheme 7

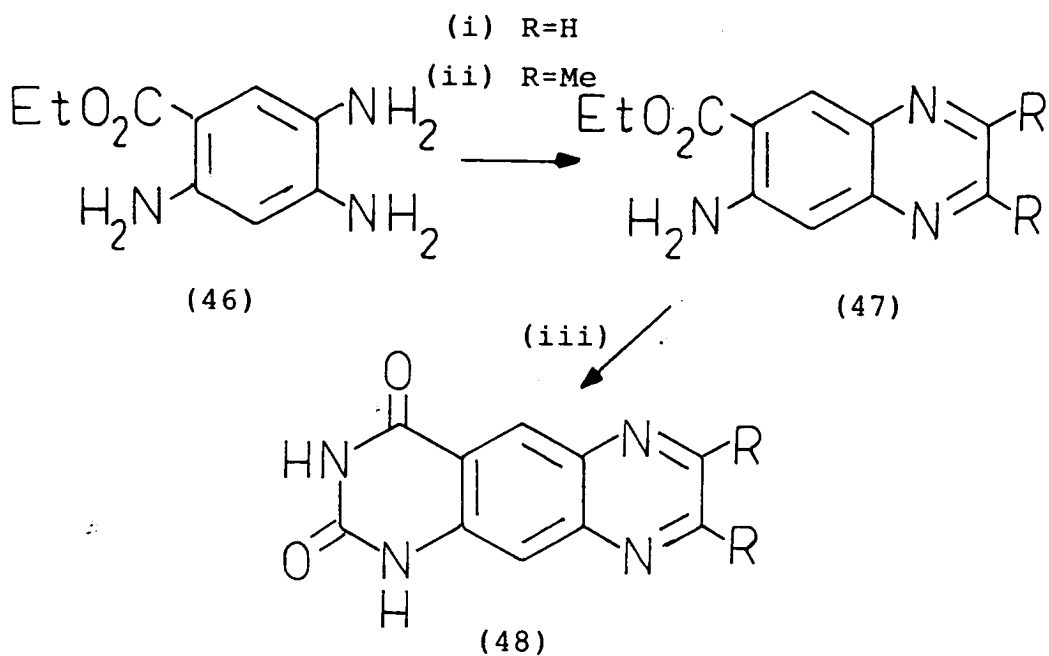


(i) NH₃, BuOH, 140-150°.

(ii) H₂, Pd-C, HCl, H₂O, CH₃OCH₂CH₂OH.

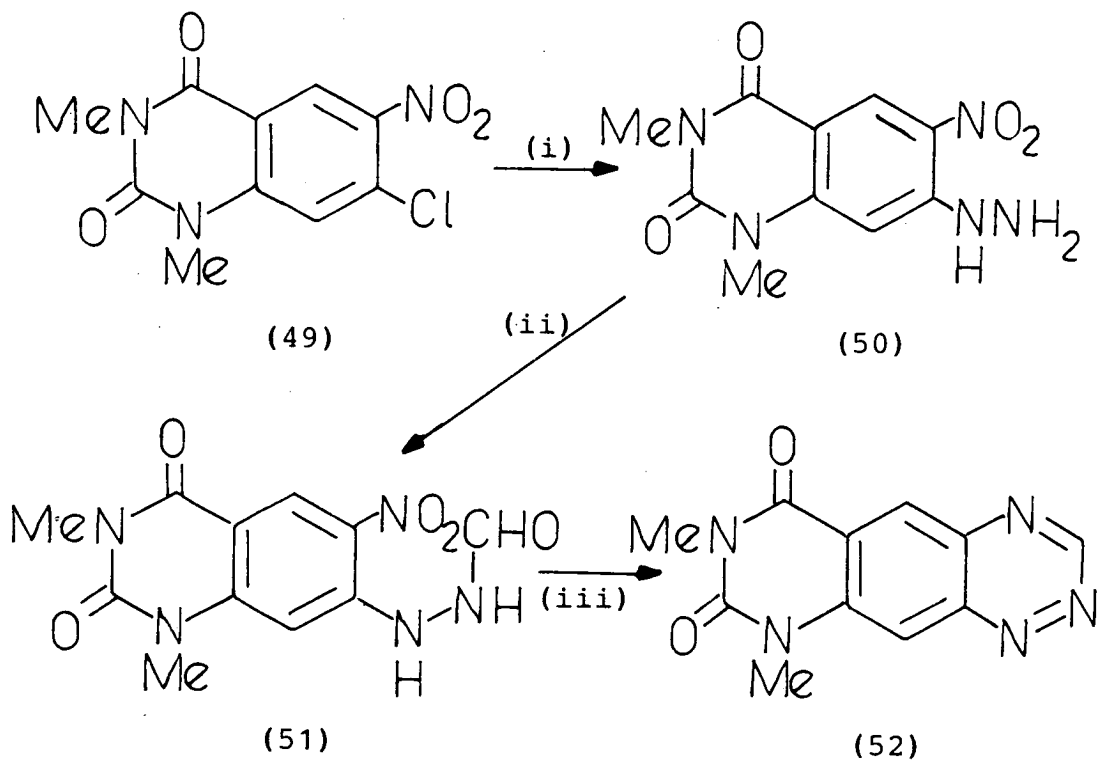
(iii) CHO.CHO.

Scheme 8



- (i) $(\text{HCO})_2$, NaHSO_3 , H_2O . $\underline{\text{R}}$
 (ii) $\text{MeCO} \cdot \text{COMe}$, H_2O . a; H
 (iii) NH_2CONH_2 , heat. b; Me

Scheme 9

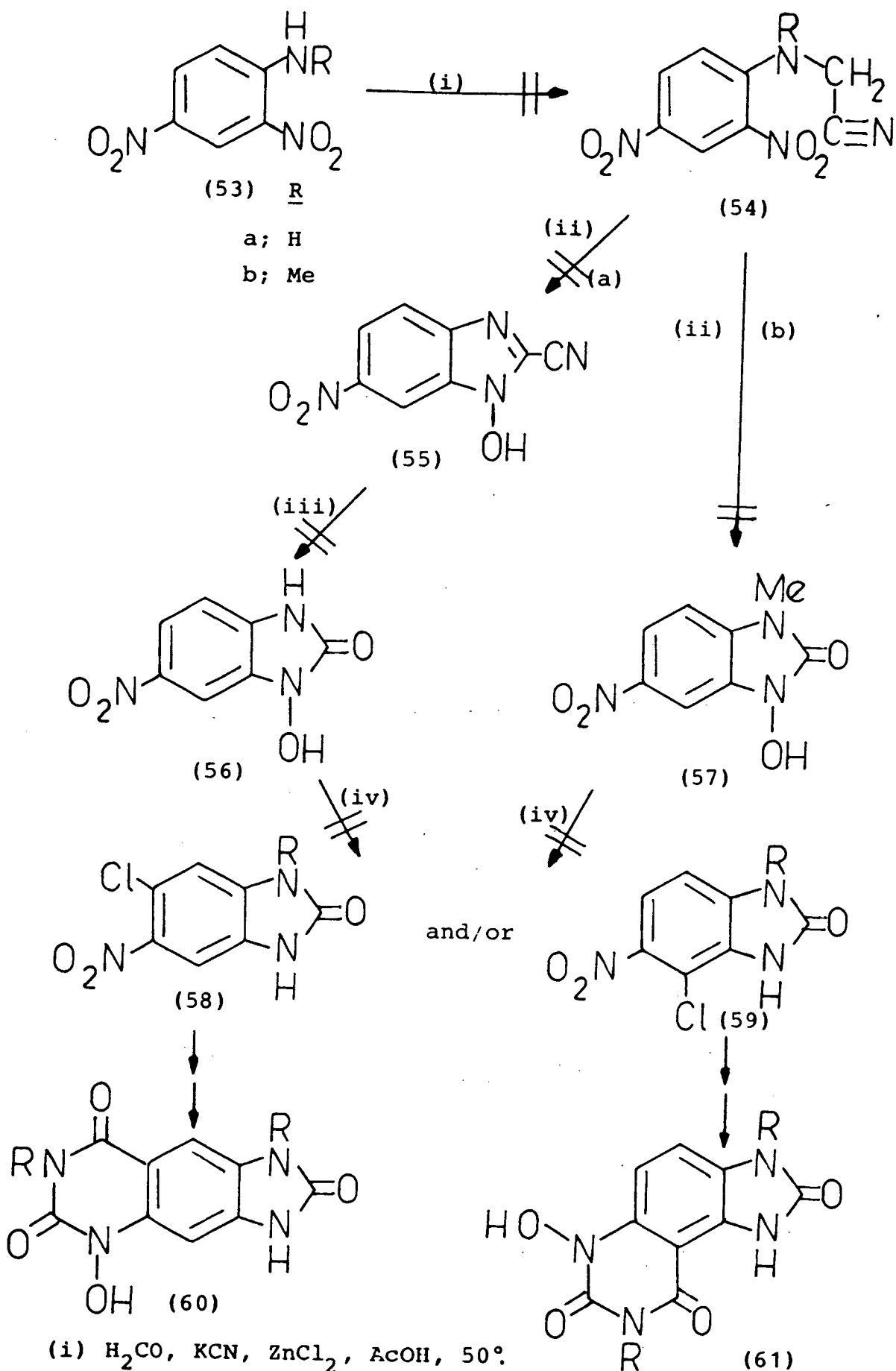


- (i) NH_2NH_2 , H_2O , EtOH , N_2 , heat.
 (ii) HCO_2H , H_2O , heat.
 (iii) H_2 , Pd-C , MeOH .

Scheme 10

Moser^{151,152} have reported the synthesis of lin-benzo-allopurinol [Scheme 6; (39)] together with (Scheme 7) the isomeric tricyclic systems (41)-(43) from indazole precursors. These workers^{151,152} have also reported (Scheme 7) the synthesis of lin-benzooxipurinol (40a) and the corresponding amino derivative (40b). Biological evaluation of these derivatives (40)-(43) for xanthine oxidase inhibitory, antiviral and cytostatic properties is underway.^{151,152}

The synthesis of 'stretched' pteridines and aza-pteridines has also been reported in the literature and can be exemplified (Scheme 8)¹⁴² by the preparation of prox-benzolumazine (45). Treatment of the quinazolinone derivative (32) with ammonia-saturated butanol at high temperature under sealed conditions gave the amino-nitroguanazolinone (34a), which on reduction and reaction with glyoxal afforded prox-benzolumazine (45). The same workers¹⁴³ had previously prepared (Scheme 9) lin-benzolumazine (48a) and the 7,8-dimethyl derivative (48b) from the hydrochloride salt of ethyl 2,4,5-triaminobenzoate (46). Treatment of the latter with glyoxal in the presence of sodium bisulphite afforded the quinoxaline derivative (47a) which on fusion with urea gave lin-benzolumazine (48a). Similarly treatment of the hydrochloride salt of the triaminobenzoate (46) with butane-2,3-dione in water gave the dimethyl-quinoxaline derivative (47b) which reacted with urea to give 7,8-dimethyl-lin-benzolumazine (48b). Schneller and Christ¹⁵³ have also reported (Scheme 10) the synthesis of lin-benzo-aza-pteridines (52) from the chloro-nitroquinazolinone derivative (49). Treatment of the latter with hydrazine gave the quinazolinone derivative (50) which

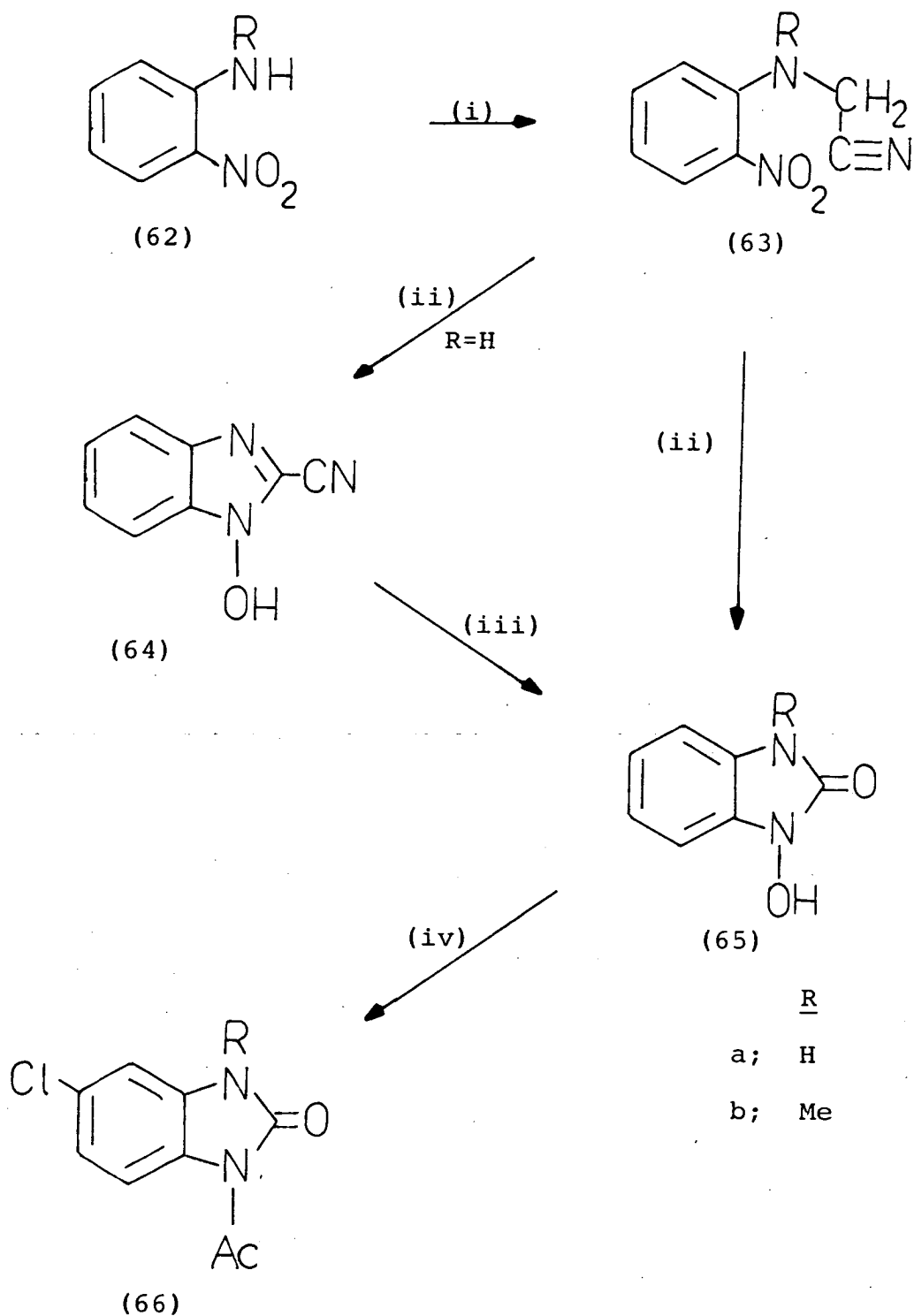


Scheme 11

reacted with formic acid to afford the formylhydrazino derivative (51). Reduction of the formylhydrazino (51) afforded the lin-benzo-aza-pteridine (52) directly, presumably via reduction of the nitro-substituent and spontaneous intramolecular cyclisation of the resulting amino intermediate.

(i) New Synthetic Approaches to N-Oxygenated 'Stretched' Purines and Related Polyazaheterocycles Based on Annulation Reactions of Nitrobenzimidazole Derivatives

As discussed earlier the synthesis of N-oxygenated 'stretched' purines and their isosteres has not been previously investigated and is of interest due to their potentially useful biological properties. The initial approach adopted (Scheme 11) involves the synthesis of ortho-chloro-nitrobenzimidazolone derivatives (58) and (59) which could be further converted into N-oxygenated lin-benzopurine and prox-benzopurine derivatives (60) and (61) respectively. The proposed synthesis of the ortho-chloro-nitrobenzimidazolone derivatives (58) and (59) involves the preparation of 2,4-dinitroaniline derivatives (54), base-catalysed cyclisation of which could give N-oxygenated benzimidazoles (56) and (57). Reaction of the latter with acetyl chloride in glacial acetic acid could then give the desired ortho-chloro-nitrobenzimidazolone derivatives (58) and/or (59). The 6-chloro-5-nitrobenzimidazolones (58) were seen as the most likely products from the reaction of the N-oxygenated benzimidazoles (56) and (57) with acetyl chloride in glacial acetic acid, due to the directing effect of the nitro substituent in these compounds.

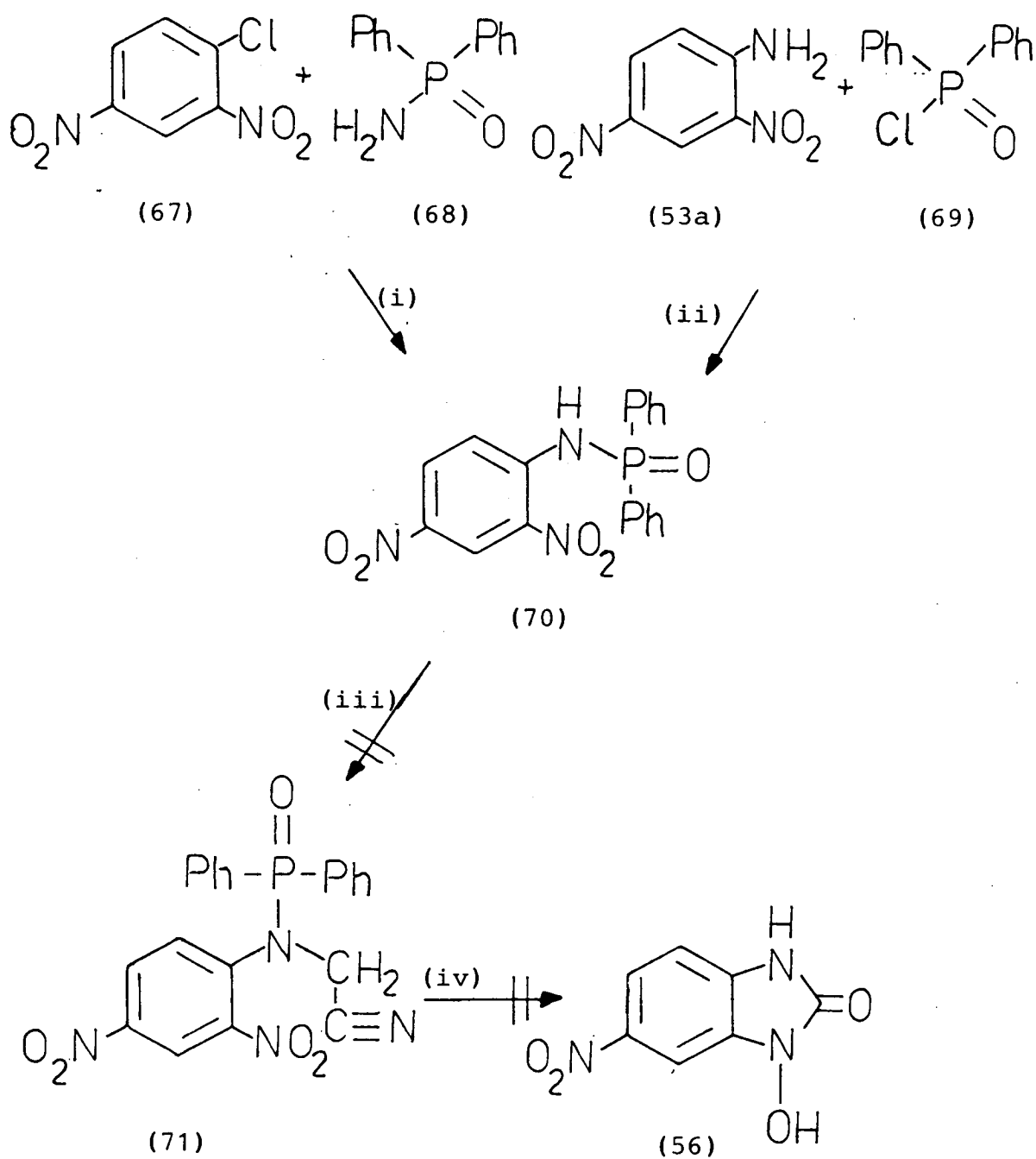


- (i) H_2CO , KCN, ZnCl_2 , AcOH, 50° .
- (ii) Na_2CO_3 , H_2O , EtOH.
- (iii) base.
- (iv) AcCl, AcOH, heat.

Scheme 12

The synthesis (Scheme 12)^{154,155} of ortho-nitroaniline derivatives (63) and their base-catalysed cyclisation¹⁵⁵ to N-oxygenated benzimidazolone derivatives (65) has been reported in the literature. Tennant and Livingstone¹⁵⁵ demonstrated that the initial product from the base-catalysed cyclisation of the unsubstituted amino-acetonitrile derivative (63a) was 2-cyano-1-N-hydroxybenzimidazole (64), which afforded the benzimidazolone (65a) on hydrolysis. These workers¹⁵⁵ also showed that heating the N-oxygenated benzimidazolone (65a) with acetyl chloride in glacial acetic acid resulted in the formation of 1-acetyl-5-chlorobenzimidazolone (66a) in good yield.

The attempted (Scheme 11) synthesis of the 2,4-dinitroaniline derivative (54a) by the reaction of 2,4-dinitroaniline (53a) with paraformaldehyde, potassium cyanide and zinc chloride in glacial acetic acid did not give the expected amino-acetonitrile derivative (54a). The observed product from this reaction was an uncharacterised yellow solid which gave analytical and mass spectral data consistent with the molecular formula $C_7H_5N_3O_4$. The i.r. spectrum of the product contained NH and nitro absorptions at 3340, 1500 and 1350 cm^{-1} , but the ^1H n.m.r. spectrum could not be obtained due to the intractable nature of the material. Acid hydrolysis of the uncharacterised solid $C_7H_5N_3O_4$ afforded an excellent recovery of 2,4-dinitroaniline (53a). The failure (Scheme 11) of the latter to react with paraformaldehyde, potassium cyanide and zinc chloride in glacial acetic acid could be due to the low basicity of the amino group in 2,4-dinitroaniline. 2,4-Dinitro-N-methylaniline (53b) is more basic than 2,4-dinitroaniline (53a) and



(i) NaOH , K_2CO_3 , C_6H_6 , heat.

(ii) NaH , Me_2NCHO

(iii) ClCH_2CN , $\text{Bu}_4\text{N}^+\text{HSO}_4^-$, NaOH , H_2O , C_6H_6 , heat or NaH , Me_2NCHO .

(iv) base.

Scheme 13

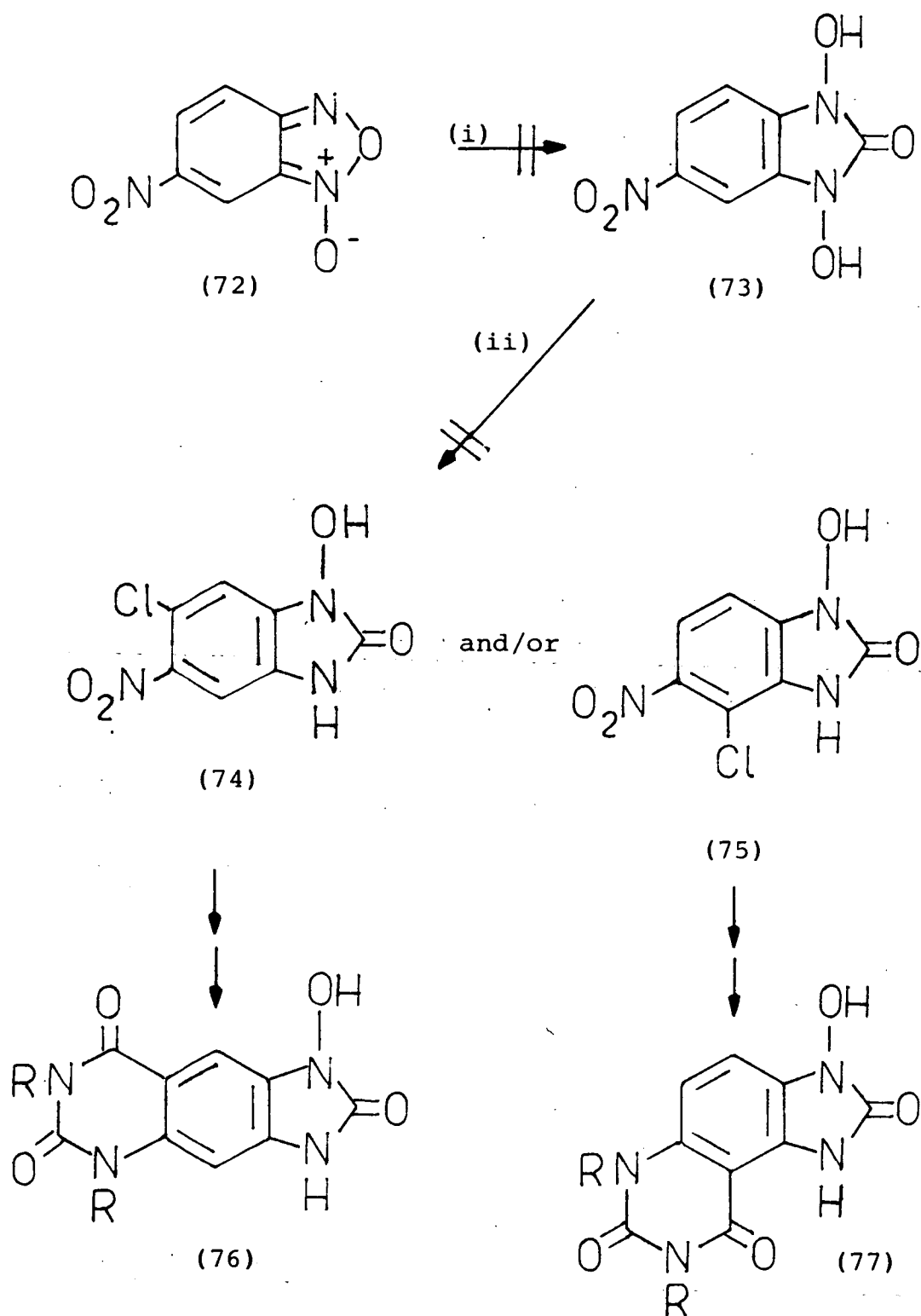
might react with paraformaldehyde, potassium cyanide and zinc chloride in glacial acetic acid to give the amino-acetonitrile derivative (54b). Base-catalysed cyclisation of the latter could then give the benzimidazolone derivative (57). Chlorination and subsequent elaboration^{of the latter} might afford N-oxygenated 'stretched' purines derivatives (60b) and/or (61b).

2,4-Dinitro-N-methylaniline [Scheme 11; (53b)] was readily prepared by the reaction of 2,4-dinitro-chlorobenzene with ethanolic methylamine as described by Le Bris.¹⁵⁶ However, treatment of 2,4-dinitro-N-methylaniline (53b) with paraformaldehyde, potassium cyanide and zinc chloride in glacial acetic acid failed to give the expected amino-acetonitrile derivative (54b). The only material isolated from this reaction was unreacted starting-material (53b). The failure of this reaction was thought to be due either to a steric effect from the N-methyl substituent in 2,4-dinitro-N-methylaniline (53b), or that the latter was still insufficiently basic to react with paraformaldehyde, potassium cyanide and zinc chloride in glacial acetic acid.

Having failed (Scheme 11) to obtain amino-acetonitrile derivatives (54) suitable for base-catalysed cyclisation to N-oxygenated benzimidazoles (56) or (57) from 2,4-dinitro-aniline derivatives (53) an alternative approach (Scheme 13) to the N-oxygenated benzimidazole (56) was investigated. The diphenylphosphinyl derivative (70) would be expected to form a stable anion on treatment with base, which could then react with chloroacetonitrile to give the amino-acetonitrile derivative (71), base-catalysed cyclisation of which should

then afford the N-oxygenated benzimidazolone (56). The synthesis of diphenylphosphinanilide by reaction of diphenylphosphinyl chloride (69) with aniline has been reported in the literature¹⁵⁷ together with the formation of diphenylphosphinyl-alkylamine derivatives on treatment of diphenylphosphinamide (68) with alkyl halides.

The initial approach (Scheme 13) to the required diphenylphosphinyl derivative (70) using 2,4-dinitrochlorobenzene (67) and the known¹⁵⁸ diphenylphosphinamide (68) was based on the method of Zwierzak and Slusarska¹⁵⁷ for the synthesis of diphenylphosphinyl-alkylamine derivatives. Thus, heating a suspension of 2,4-dinitrochlorobenzene (67), diphenylphosphinamide (68), sodium hydroxide and potassium carbonate in benzene afforded a low yield of a cream crystalline solid which gave analytical and mass spectral data consistent with the molecular formula $C_{18}H_{14}N_3O_5P$. The i.r. spectrum of this product showed absorptions at 1530, 1510, 1345 and 1330 cm^{-1} due to two nitro groups, together with an NH absorption at 3280 cm^{-1} . The ^1H n.m.r. spectrum contained resonances due to thirteen aromatic protons along with a singlet resonance at $\delta 9.44$ attributed to an NH substituent. The observed analytical and spectroscopic properties allowed the formulation of the cream solid as the expected 2,4-dinitrophenyl-phosphinamide derivative (70). However because of the low yield of the product (70) obtained alternative methods for its preparation were investigated. Heating 2,4-dinitroaniline (53a) with diphenylphosphinyl chloride (69) in benzene gave only unreacted 2,4-dinitroaniline (53a). However reaction of diphenylphosphinyl chloride (69) with the sodium salt of 2,4-



(i) H_2CO , KOH , MeOH , H_2O , $40-50^\circ$.

(ii) AcCl , AcOH , heat.

Scheme 14

dinitroaniline (53a) gave a good yield (75%) of the N-(2,4-dinitrophenyl)diphenylphosphinamide (70). This method for the preparation of the diphenylphosphinyl derivative (70) not only goes in better yield than that reported above, it also avoids the use of the potential skin irritant 2,4-dinitrochlorobenzene (67).

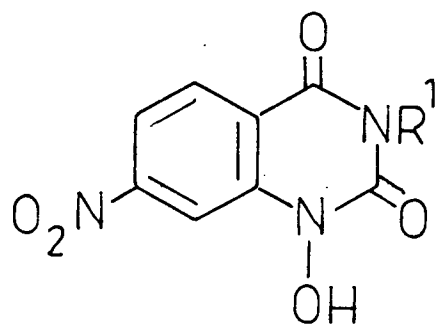
Reaction of the 2,4-dinitrophenyl-phosphinyl derivative (70) with chloroacetonitrile did not however give the expected tertiary amine derivative (71). In fact reaction of the phosphinyl derivative (70) with chloroacetonitrile under phase-transfer catalytic conditions using tetrabutylammonium hydrogen sulphate gave only unreacted phosphinamide (70) and a multicomponent mixture, shown by t.l.c. to contain 2,4-dinitroaniline (53a), presumably from hydrolysis of the starting-material (70). Similarly, reaction of chloroacetonitrile with the sodium salt of the phosphinamide (70), preformed using sodium hydride, gave only an excellent yield of unreacted 2,4-dinitrophenyl-phosphinamide (70). The failure of the sodium salt of the phosphinamide (70) to react with chloroacetonitrile was unexpected and may be due to the delocalisation of the anionic charge into the diphenylphosphinyl moiety, thus stabilising and reducing the reactivity of the anion. The synthesis (Scheme 13) of the benzimidazolone (56) required for further elaboration to a 'stretched' purine system was prevented by the failure to effect the preparation of the tertiary amino-acetonitrile derivative (71).

In a further attempt (Scheme 14) to synthesise ortho-chloro-nitrobenzimidazolones e.g. (74) and/or (75) for further elaboration to N-oxygenated 'stretched' purine derivatives

(76) and/or (77) an attempt was made to obtain 1,3-dihydroxy-5-nitrobenzimidazolone (73). Tennant and Davidson¹⁵⁹ have shown that reaction of 1,3-di-N-hydroxybenzimidazolone with acetyl chloride in glacial acetic acid gives chlorine substitution in the benzene ring and it was hoped that the nitro derivative (73) would behave in a similar manner to give either of the nitro-chlorobenzimidazolone derivatives (74) or (75). Mallory and Varimbi¹⁶⁰ have reported the synthesis of 6-nitrobenzofuroxan (72) by diazotisation of 2,4-dinitroaniline followed by reaction with sodium azide and Ley and Seng¹⁶¹ demonstrated the preparation of 1,3-di-N-hydroxybenzimidazolones from benzofuroxan derivatives using formaldehyde under base-catalysed conditions.

In practice diazotisation of 2,4-dinitroaniline followed by reaction with sodium azide gave only a low yield (40%) of 6-nitrobenzofuroxan (72).¹⁶⁰ Treatment of the latter with aqueous formaldehyde in the presence of methanolic potassium hydroxide gave only intractable mixtures from which no identifiable material could be obtained. The failure of the reaction of the benzofuroxan (72) with formaldehyde to give the N-oxygenated benzimidazolone (73) precluded the investigation into the synthesis of the ortho-chloro-nitrobenzimidazolones (74) and/or (75).

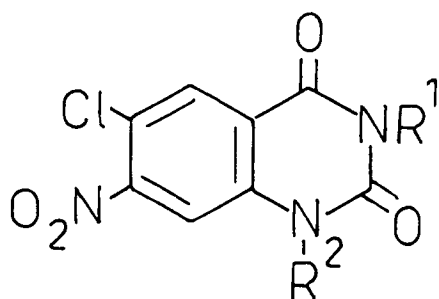
The failure to effect the synthesis (Schemes 11, 13 and 14) of ortho-chloro-nitrobenzimidazolone derivatives prevented the proposed investigations into their further elaboration to N-oxygenated 'stretched' purines (60), (61), (76) and (77).



(78)

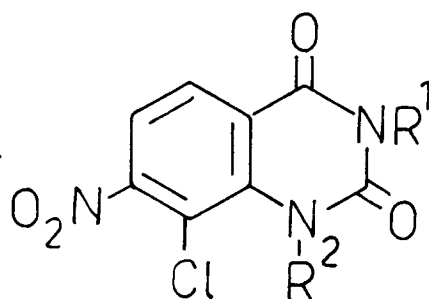


(i)

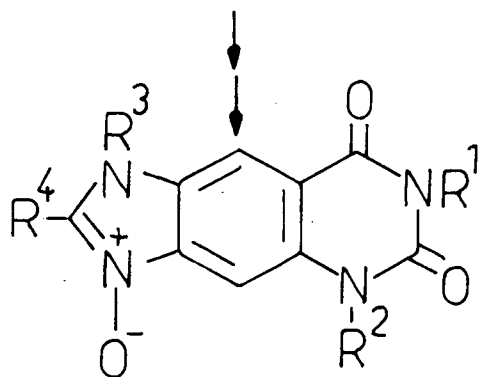


(79)

and/or

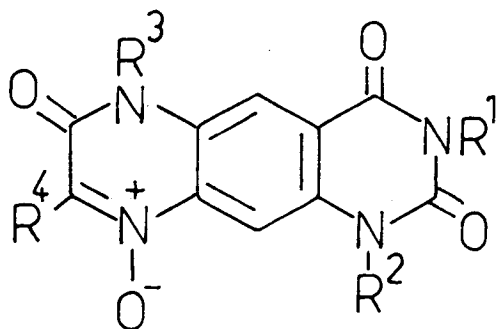


(80)

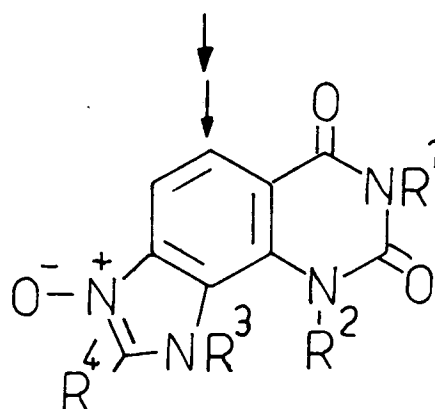


(81)

and

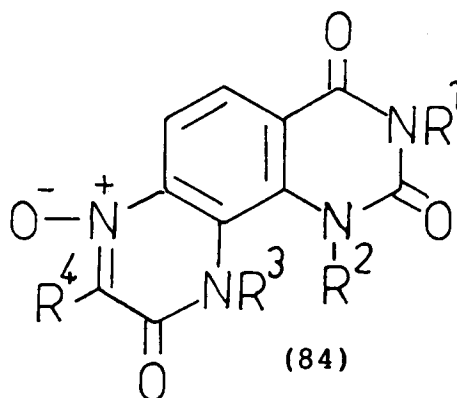


(83)



(82)

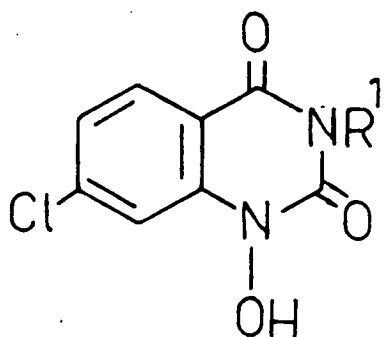
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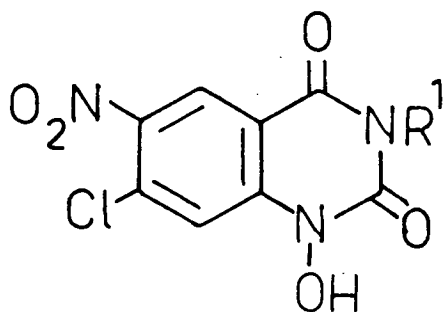
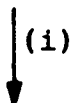
(84)

(i) AcCl, AcOH, heat.

Scheme 15

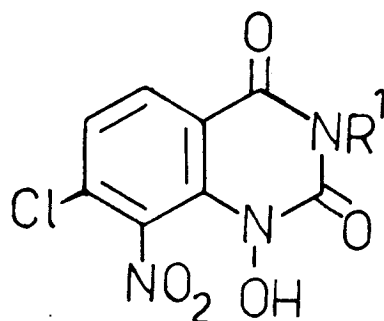


(85)

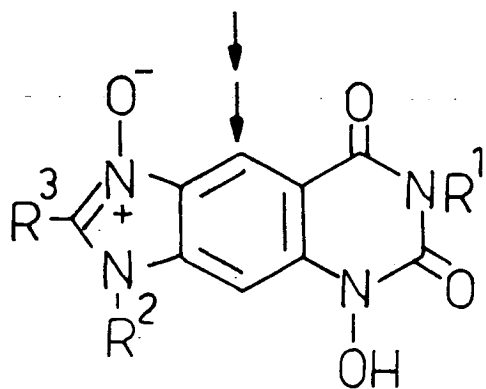


(86)

and/or

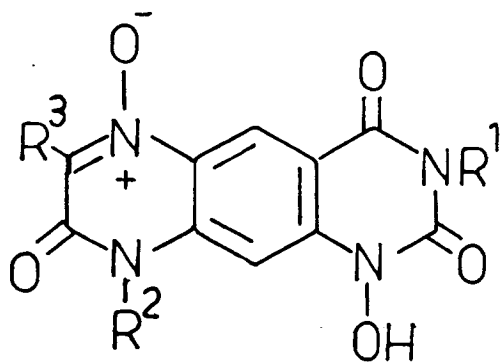


(87)

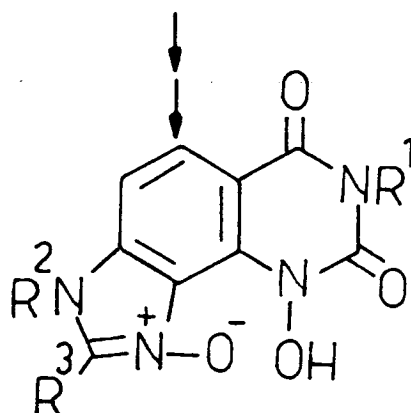


(88)

and

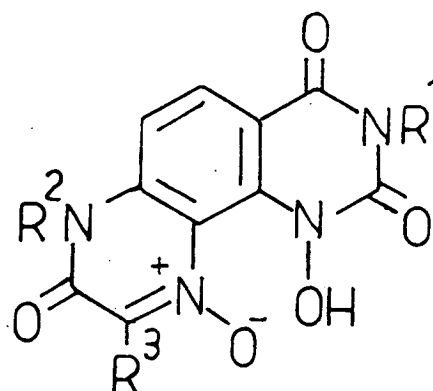


(90)



(89)

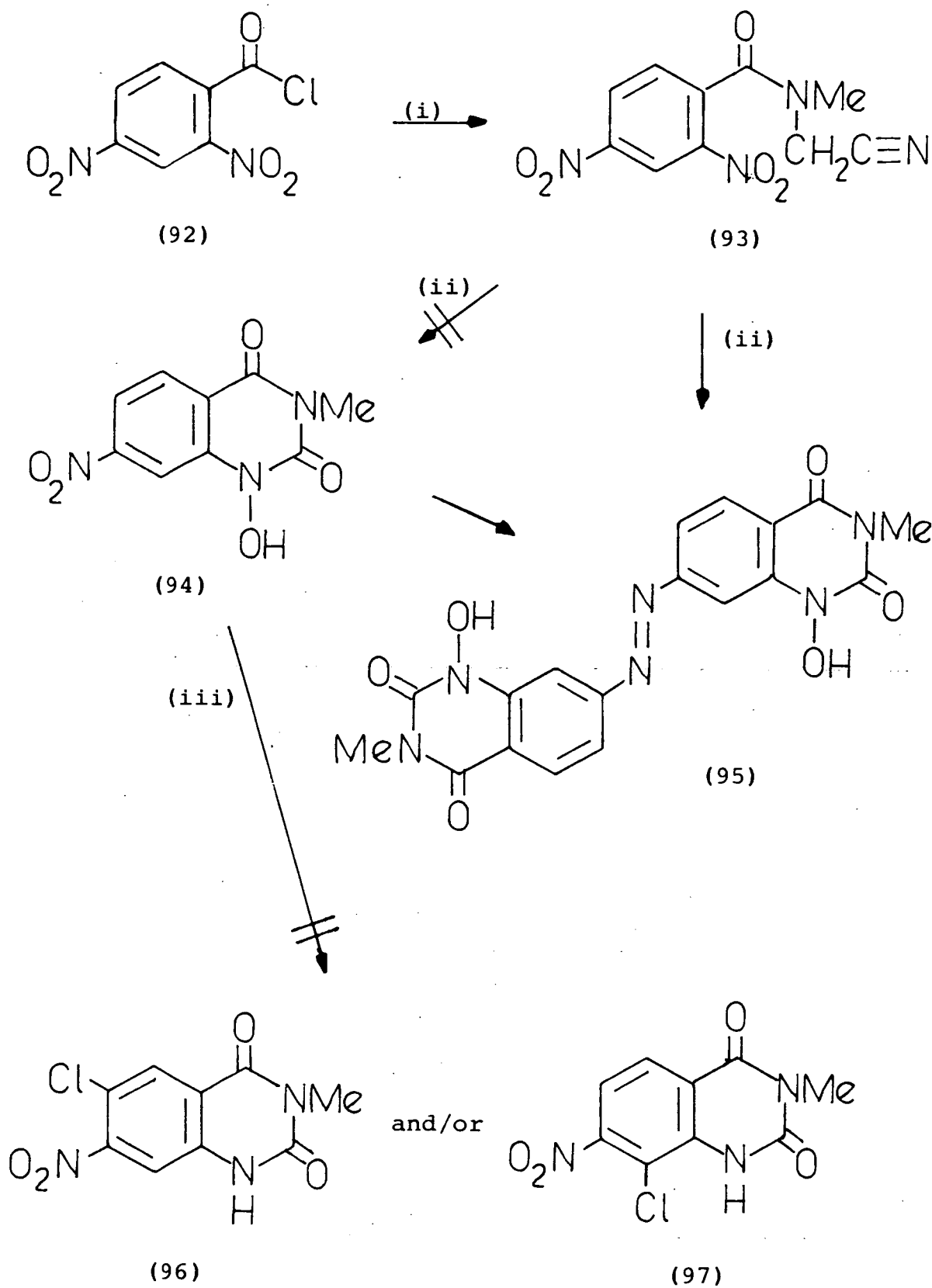
and



(91)

(1) HNO_3 , H_2SO_4 .

Scheme 16



(i) $\text{MeNHCH}_2\text{CN} \cdot \text{HCl}$, NaOAc , AcOH .

(ii) NaOEt , EtOH , heat.

(iii) AcCl , AcOH , heat.

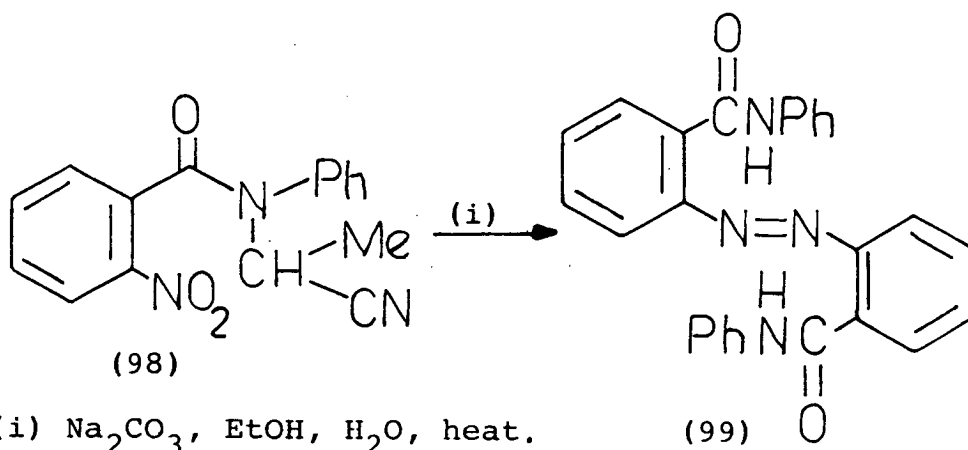
(ii) New Synthetic Approaches to N-Oxygenated 'Stretched' Purines and Pteridines Based on Annulation Reactions of Nitroquinazoline Derivatives

As approaches to the synthesis of N-oxygenated 'stretched' purines via suitably substituted benzimidazole derivatives had proved unsuccessful, alternative strategies for the synthesis of these compounds and their pteridine analogues were investigated. The ortho-chloro-nitroquinazolinediones (79) and (80), which could be obtained by chlorination of N-hydroxy-nitroquinazolinediones (78), were selected as suitable starting-materials for the preparation of 'stretched' purine and pteridines N-oxides (81)-(84) (Scheme 15). Alternatively (Scheme 16) ortho-chloro-nitroquinazolinediones (86) and (87) could be prepared by nitration of chloro-N-hydroxyquinazolinediones (85) and then elaborated to the required N-oxides (88)-(91).

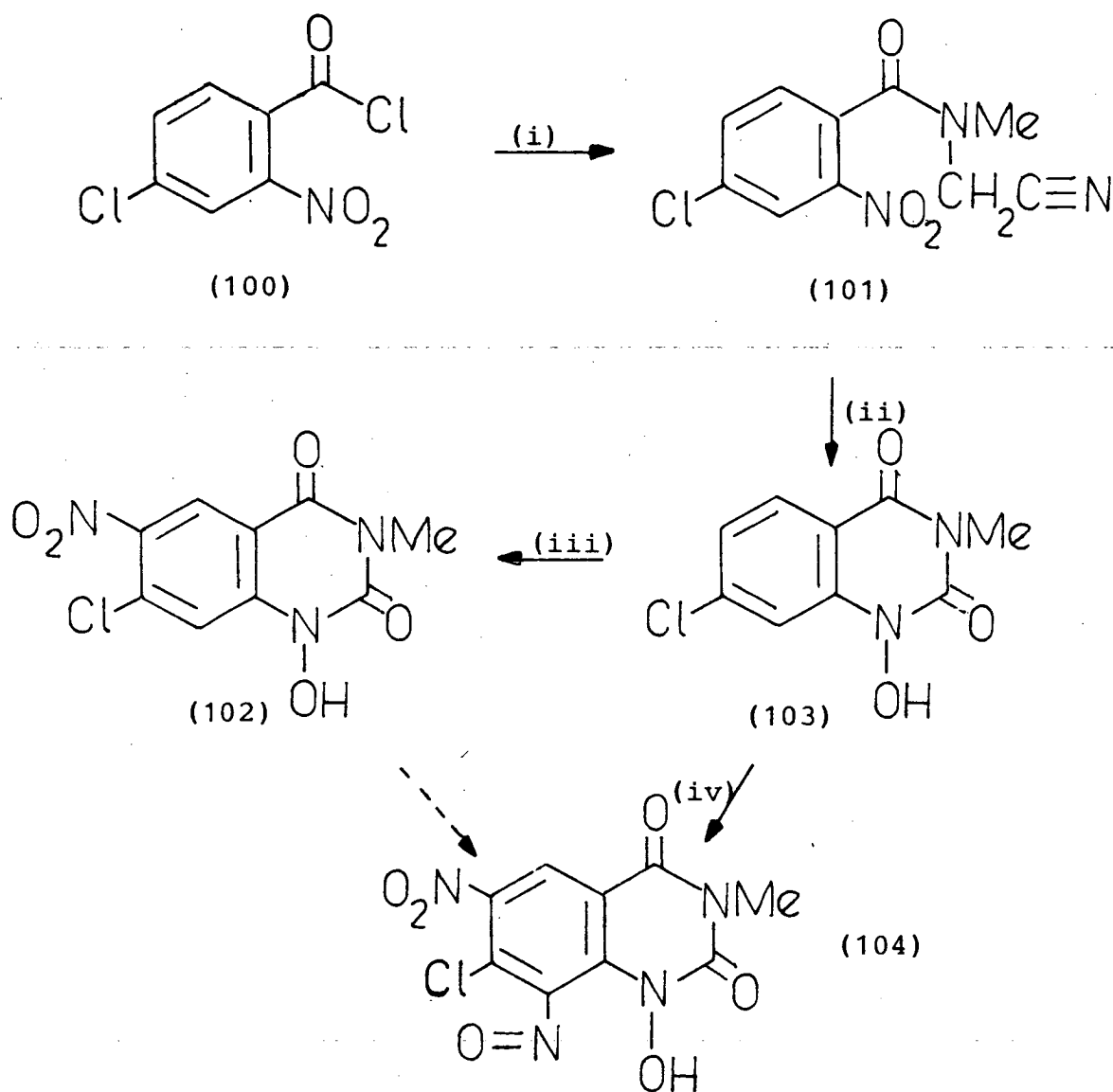
The initial strategy adopted (Scheme 17) involved the preparation of ortho-chloro-nitroquinazolinediones (96) and/or (97) via chlorination of the N-hydroxy-nitroquinazolinedione (94). The latter should be available from base-catalysed cyclisation of the 2,4-dinitrobenzoylaminoacetonitrile derivative (93). As discussed earlier base-catalysed cyclisation of this type for the synthesis of N-oxygenated quinazolines from ortho-nitrobenzoylaminoacetonitrile derivatives is well known.⁴³

In practice treatment of the readily available¹⁶² 2,4-dinitrobenzoyl chloride (92) with N-methylaminoacetonitrile hydrochloride in glacial acetic acid in the presence of fused sodium acetate gave a high yield of a crystalline solid whose

analytical and mass spectral data were in accord with the 2,4-dinitro-benzoylaminoacetonitrile structure (93). The i.r. spectrum of this product contained absorptions due to a carbonyl and nitro substituent at 1660, 1525 and 1350 cm^{-1} , but lacked any absorption due to a cyano-substituent. However it is known⁶² that i.r. cyano absorption can be very weak or totally non-observed and this phenomenon has been observed for imidazoylaminoacetonitrile derivatives in chapter two. Curiously the ^1H n.m.r. spectrum of this compound (93) at room temperature showed signals due to the protons of two methylene and two N-methyl substituents and not one methylene and one N-methyl substituent as expected. However at 87° the ^1H n.m.r. spectrum contains only the expected proton resonances and these features can be explained in terms of the benzoylaminoacetonitrile (93) existing as two distinct conformational isomers at room temperature. At 87° the temperature is high enough to overcome the energy barrier to free rotation about the amide bond. This energy barrier accounts for the presence of the two conformational isomers at room temperature and this feature was also observed for the imidazoylaminoacetonitrile [Chapter 2; Scheme 11; (31)]. The attempted base-catalysed cyclisation of the 2,4-dinitrobenzoylaminoacetonitrile (93) did not however give the expected N-hydroxy-nitroquinazoline-dione (94). Heating a solution of the benzoylaminoacetonitrile (93) in ethanol with sodium ethoxide afforded a good yield of a yellow solid which gave accurate mass data consistent with the molecular formula $\text{C}_{18}\text{H}_{14}\text{N}_6\text{O}_6$. The observed analytical data was consistent with a monohydrate of a compound with this molecular formula. The i.r. spectrum of



Scheme 18



- (i) $\text{MeNHCH}_2\text{CN} \cdot \text{HCl}$, NaOAc , AcOH .
- (ii) NaOEt , EtOH, heat.
- (iii) HNO_3 , H_2SO_4 , heat, 20min.
- (iv) HNO_3 , H_2SO_4 , heat, 1h.

Scheme 19

this compound contained absorptions due to two carbonyl bands at 1710 and 1665 cm^{-1} , together with broad absorption centred at 3400 cm^{-1} , due to OH substituents. The ^1H n.m.r. spectrum of the product could not be obtained due to its high insolubility in deuterated dimethylsulphoxide. However the observed analytical, accurate mass and i.r. spectral data of the yellow product are consistent with a monohydrate of the azo-di-N-hydroxyquinazolinedione derivative (95). In an attempt to gain further evidence for this structure an attempt was made to obtain its acetyl derivative by heating the compound (95) with acetic anhydride. The only isolated product from this reaction was an intractable mixture which was not further investigated.

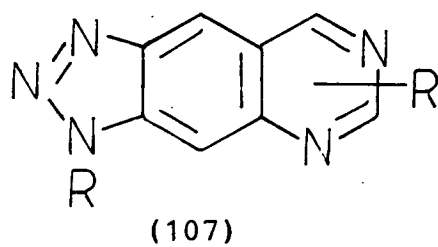
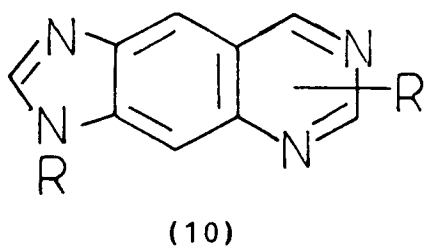
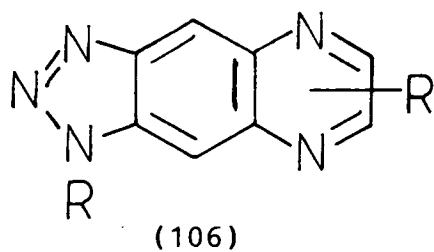
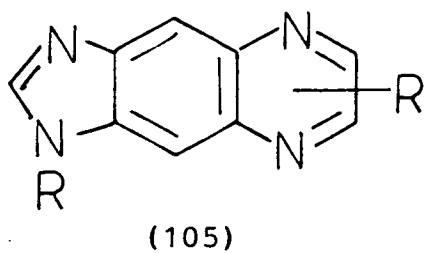
The formation of the azo-di-N-hydroxyquinazalinedione (95) was unexpected, but could be explained by an initial base-catalysed cyclisation of the benzoylaminoacetonitrile (93) to an intermediate N-hydroxy-nitroquinazolinedione (94). Under the basic conditions employed this could undergo a reductive dimerisation to the azoxy-quinazolinedione (95). The formation of azo-benzamide derivatives from nitrobenzamide derivatives under basic conditions is known and is exemplified (Scheme 18)⁶³ by the aqueous ethanolic sodium carbonate catalysed dimerisation of the nitrobenzamide (98) to the azo-dimer (99). Due to the formation of the azo-di-N-hydroxy-quinazolinedione (95) as opposed to the desired N-hydroxy-nitroquinazolinedione (94), the proposed investigation into the synthesis of N-oxygenated 'stretched' purines and pteridines, as outlined in the general Scheme 15, was not taken any further.

However attempts were made to obtain ortho-chloro-nitroquinazolinedione derivatives (86) and/or (87) by nitration of the known chloro-N-hydroxyquinazolinedione [Scheme 19; (103)]¹⁶³ to provide the starting-material required for the synthesis of 'stretched' purine and pteridine N-oxides (88)-(91) as outlined in Scheme 16.

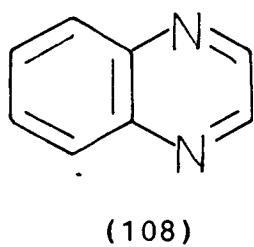
In practice (Scheme 19) treating 4-chloro-2-nitrobenzoyl chloride (100)¹⁶⁴ with N-methylaminoacetonitrile afforded a high yield (91%) of the 4-chloro-2-nitrobenzoylaminoacetonitrile derivative (101).¹⁶³ Base-catalysed cyclisation of the latter using sodium ethoxide gave the N-hydroxyquinazolinedione (103),¹⁶³ also in high yield. The attempted nitration of the N-hydroxyquinazolinedione (103) in sulphuric acid using fuming nitric acid at 100° gave a brown crystalline solid in low yield, which proved difficult to handle. However the mass spectral data obtained for this product was consistent with the molecular formula $C_9H_6ClN_3O_5$. The i.r. spectrum of the product contained absorption bands at 1735, 1540 and 1340 cm^{-1} , corresponding to carbonyl and nitro substituents, and the presence of a broad band at 3700-3200 cm^{-1} was indicative of a hydroxyl substituent in the product. The 1H n.m.r. spectrum of the product showed signals due to the presence of two aromatic protons, as singlets at δ 8.51 and 7.33, and singlet resonances at δ 12.01 and 3.32 corresponding to an OH and an N-methyl substituent were also observed. The above spectroscopic features of the brown crystalline solid allowed its tentative formulation as the expected ortho-chloro-nitroquinazolinedione derivative (102). In an attempt to improve the yield of this compound by nitration of the chloro-N-hydroxyquinazolinedione

(103), the reaction of the latter with fuming nitric acid was repeated using an excess of fuming nitric acid and heating the reaction mixture for a longer period of time. However under these harsher conditions the observed product was not the ortho-chloro-N-hydroxy-nitroquinazolinedione (102). The only material isolated was a very low yield of a colourless crystalline solid which gave analytical and mass spectral data consistent with the molecular formula $C_9H_5ClN_4O_6$. This product was also difficult to purify, but its analytical and spectroscopic properties allowed its formulation as the 6-nitro-8-nitrosoquinazolinedione (104). In particular the 1H n.m.r. spectrum of the quinazolinedione (104) contained only singlet resonances due to one high field aromatic proton at $\delta 8.75$ together with a signal due to an N-methyl substituent. The 8-nitrosoquinazolinedione structure (104) was assigned by comparison with the 1H n.m.r. spectrum of the ortho-chloro-nitroquinazolinedione (102), in which the aromatic proton at H-5 shows a resonance at $\delta 8.51$, presumably due to the proximity of the nitro substituent at position 6 of the quinazolinedione ring.

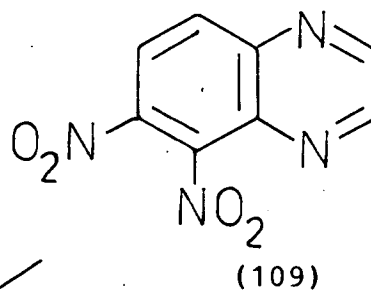
Formation (Scheme 19) of the 6-nitro-8-nitrosoquinazolinedione (104) probably arises from the initial formation of the nitroquinazolinedione derivative (102) which reacts further with the excess fuming nitric acid present in the reaction mixture. Due to the relatively low yield of the nitroquinazolinedione (102) obtained on nitration of the chloro-N-hydroxyquinazolinedione (103) and the formation of the nitrosoquinazolinedione derivative (104) under more vigorous nitration



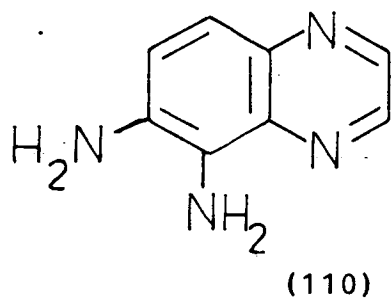
Scheme 20



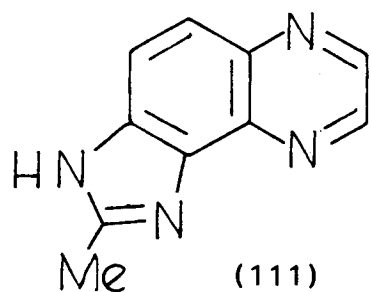
(i) →



(ii) ↘



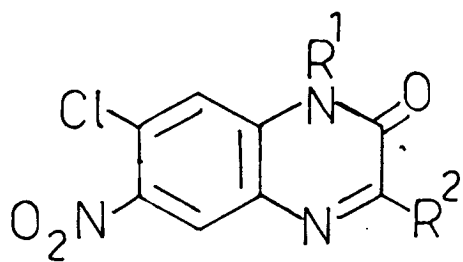
+



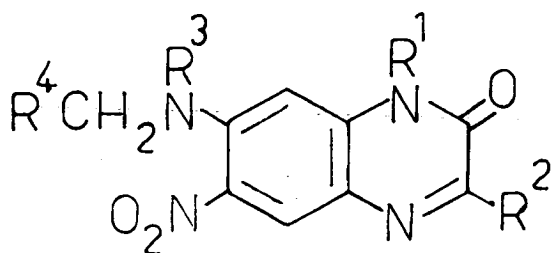
(i) HNO_3 , H_2SO_4 , heat.

(ii) Fe, AcOH, heat.

Scheme 21

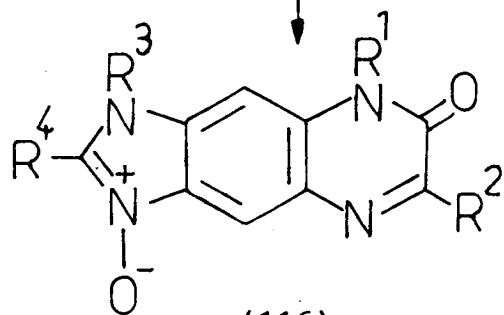


(112)



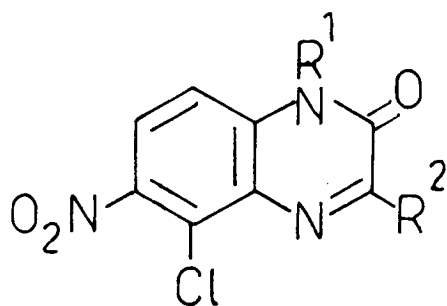
(114)

(i) $\downarrow -\text{H}_2\text{O}$

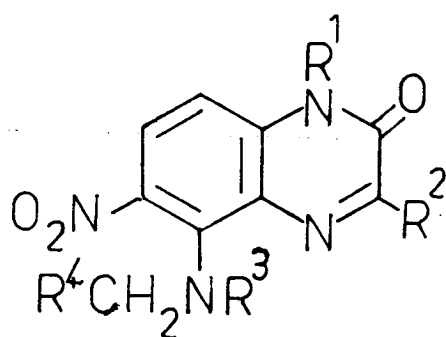


(116)

(i) base.

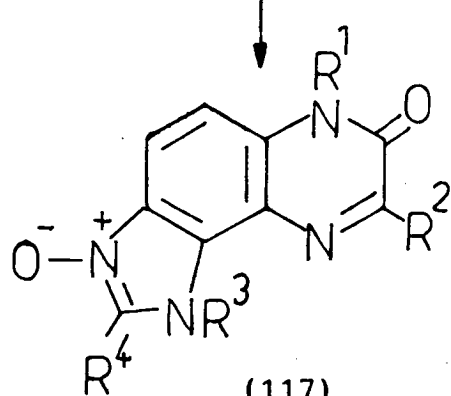


(113)



(115)

(i) $\downarrow -\text{H}_2\text{O}$



(117)

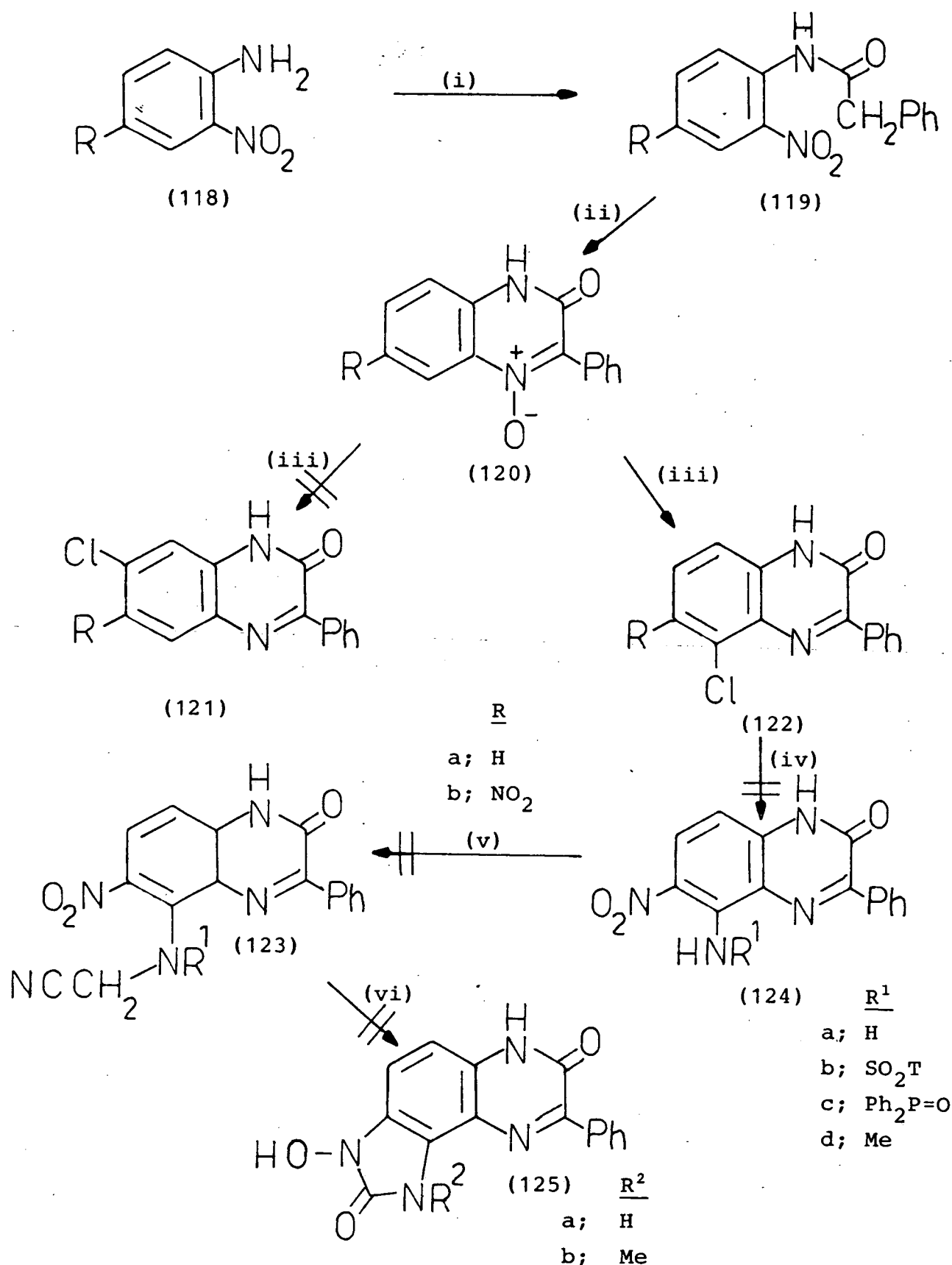
Scheme 22

conditions, the proposed investigation into the synthesis of 'stretched' purine and pteridine N-oxides (e.g. Schemes 15 and 16) was not taken any further at this time.

(iii) New Synthetic Approaches to N-Oxygenated 'Stretched' Purine Azalogues Based on Annulation Reactions of Nitroquinoxaline Derivatives

The synthesis (Scheme 20) of imidazo-quinoxalines (105) and triazolo-quinoxalines (106) and their N-oxygenated derivatives are of interest because they are isosteric with 'stretched' purine (10) and aza-purine (107) derivatives and may possess interesting biological properties. Dewar and Maitlis¹⁶⁵ have reported (Scheme 21) the synthesis of the non-linear imidazo-quinoxaline (111) as the product of a powdered iron-catalysed reduction of the dinitroquinoxaline (109) in glacial acetic acid. The diaminoquinoxaline (110) was also isolated from the reduction of the dinitroquinoxaline (109) with iron in acetic acid and the imidazoquinoxaline (111) presumably arises from the diamino-derivative (110) on reaction with acetic acid. However, N-oxygenated derivatives of imidazoquinoxalines do not appear to have been reported in the literature to date and are of particular interest in view of the utility of such compounds as precursors for the synthesis of other potentially biologically active imidazo-quinoxalines. The N-oxygenated derivatives of these compounds may also possess interesting biological properties in their own right.

The initial approach adopted (Scheme 22) for the preparation of N-oxygenated imidazoquinoxalines (116) and/or (117)



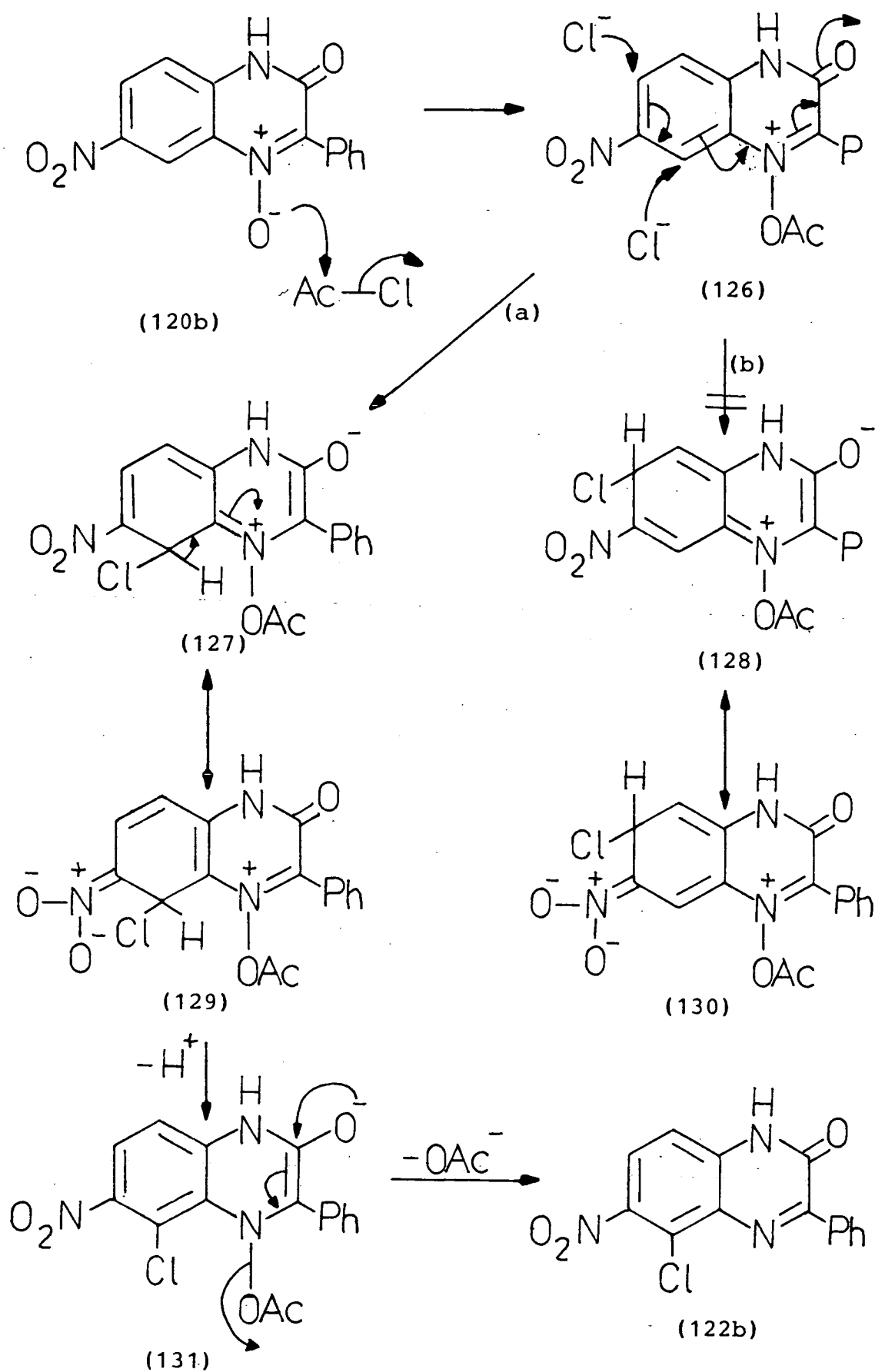
- (i) PhCH₂COCl, C₆H₆, heat.
(ii) KOH, H₂O, pyridine heat.
(iii) AcCl, AcOH, heat.
(iv) RNH₂, Me₂NCHO or RNH₂ liq. for R=H.
(v) H₂CO, KCN, ZnCl₂, AcOH, 50°.
(vi) base.

Scheme 23

involved the synthesis of ortho-chloro-nitroquinoxalinone derivatives (112) and/or (113), amination of which could provide amino-nitroquinoxaline derivatives (114) and/or (115). Base-catalysed cyclisation of the latter would then afford imidazoquinoxalinone N-oxides (116) and/or (117). Base-catalysed cyclisations of this type for ortho-nitroaniline derivatives are well known⁴³ and have been discussed at length in chapters one to three.

The synthesis (Scheme 23) of the chloro-quinoxalinone derivative (121a) by chlorination of the quinoxalinone N-oxide (120a) using acetyl chloride in glacial acetic acid has been demonstrated by Mason and Tennant.¹⁶⁶ These workers¹⁶⁶ also prepared the nitroquinoxalinone N-oxide (120b) and it was anticipated in the current investigations that chlorination of the latter would provide the ortho-chloro-nitroquinoxaline derivatives (121b) and/or (122b), suitable for further elaboration to N-oxygenated imidazoquinoxalinones.

In practice (Scheme 23) the reaction of 2,4-dinitroaniline (118b) with phenylacetyl chloride afforded a quantitative yield of the acetanilide (119b).¹⁶⁶ Base-catalysed cyclisation of the latter afforded the known quinoxalinone N-oxide (120b) in good yield. Reaction of this product (120b) with acetyl chloride in glacial acetic acid under reflux afforded a good yield of a yellow-brown crystalline solid which gave accurate mass data consistent with the molecular formula $C_{14}H_8ClN_3O_3$. The i.r. spectrum of the product showed NH/OH absorption at 3200-2700 cm^{-1} together with carbonyl and nitro absorption at 1670, 1530 and 1345 cm^{-1} . The 1H n.m.r. spectrum contained only resonances due to seven aromatic protons including two

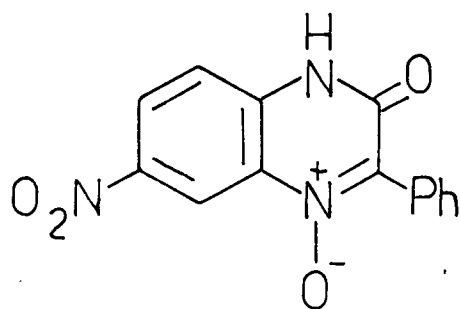


Scheme 24

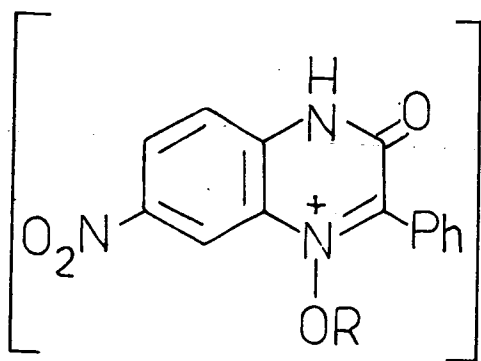
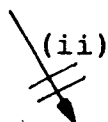
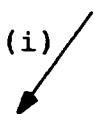
one-proton doublets centered at δ 8.09 and 7.35. The mass spectral and spectroscopic features of the product allowed its formulation as 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b). In particular the two one-proton doublets in the ^1H n.m.r. spectrum suggested the 5-chloro-6-nitro-structure (122b). If the product had been the alternative 7-chloro-6-nitroquinoxalinone (121b), the ^1H n.m.r. spectrum would have contained only two singlet proton resonances corresponding to H-5 and H-6 of the quinoxalinone ring.

The proposed mechanism for the chlorination of the N-hydroxyquinoxalinone (120b) is detailed in Scheme 24. The reaction of the latter with acetyl chloride initially gives the corresponding acetyl derivative (126) by nucleophilic displacement of the chlorine substituent. Attack by the resulting chloride ion on the benzene ring could then give either of the chlorinated intermediate quinoxalinone derivatives (127) or (128). The latter can be resonance stabilised by delocalisation of the negative charge into the nitro substituent i.e. (127) \leftrightarrow (129) and (128) \leftrightarrow (130). The preference for the formation of the 5-chloro-6-nitroquinoxalinone (122b) can be explained by the more efficient resonance stabilisation of the intermediate adduct (127) \leftrightarrow (129). Loss of H^+ from the intermediate quinoxalinone adduct (127) followed by deacetylation affords the chloro-nitroquinoxalinone product (122b).

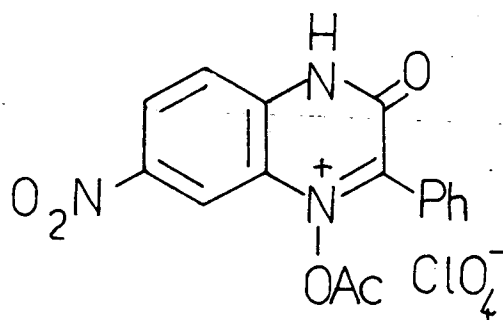
Two other solid products were isolated from the reaction of the nitroquinoxalinone N-oxide (120b) with acetyl chloride in glacial acetic acid. Both products were isolated by flash-chromatography and had melting points of 122° and 114°



(120b)



(132)

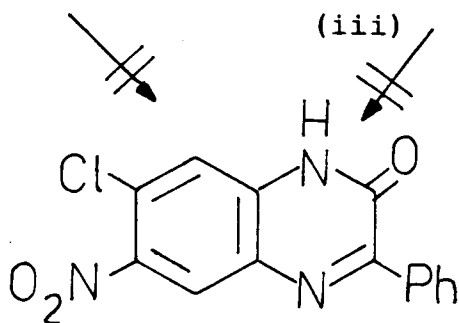


(133)

R

a; $\text{CH}_3\text{CH}_2\text{CO}$

b; $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2$

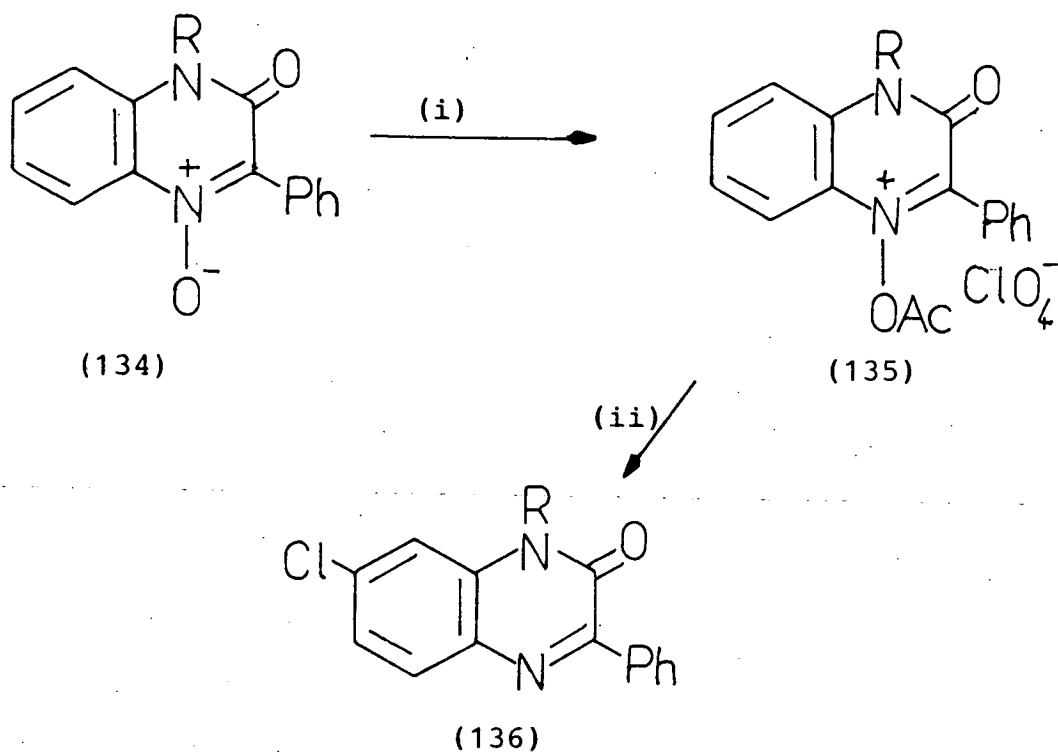


(121b)

(i) $\text{CH}_3\text{CH}_2\text{COCl}$, $\text{CH}_3\text{CH}_2\text{CO}_2\text{H}$, heat or $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{Cl}$, Me_2NCHO .
heat.

(ii) Ac_2O , AcOH , HClO_4 .

(iii) HCl .



(i) Ac_2O , HClO_4 , AcOH .

(ii) HCl .

Scheme 26

respectively. The higher melting product was shown to be N-acetyl-2,4-dinitroaniline¹⁶⁷ by combustion analysis. The i.r., ¹H n.m.r. and mass spectral data for the product confirmed the assigned structure. The lower melting solid gave analytical data and mass, i.r. and ¹H n.m.r. spectral data consistent with N,N-diacetyl-2,4-dinitroaniline¹⁶⁸ and both these products were presumed to arise from 2,4-dinitroaniline (118b) present as an impurity in the nitroquinoxalinone N-oxide (120b).

Attempts were made (Scheme 25) to direct the chlorination of the nitro-quinoxalinone N-oxide (120b) to give the 7-chloro-6-nitroquinoxalinone (121b). The initial approach involved using a bulkier acid chloride which could give the 7-chloro-6-nitroquinoxalinone (121b) by steric hindrance of the 5-position in the quinoxalinone derivative (120b) on formation of the intermediate adduct (132). In practice (Scheme 25) reaction of the nitroquinoxalinone N-oxide (120b) with propionyl chloride in propionic acid gave only a low yield of the 5-chloro-6-nitroquinoxalinone [Scheme 23; (122b)] and an intractable mixture. The reaction (Scheme 25) of nitroquinoxalinone N-oxide (120b) with toluene-*p*-sulphonyl chloride (tosyl chloride) in dimethylformamide also failed to give the 7-chloro-6-nitroquinoxalinone (121b). The only product isolated from this reaction was unreacted nitroquinoxalinone N-oxide (120b). The reaction (Scheme 26) of quinoxalinone N-oxides (134) with acetic anhydride in the presence of perchloric acid is known¹⁶⁹ to give perchlorate salts (135) and that these on reaction with hydrochloric acid afford chloroquinoxalinone derivatives (136). Therefore, an

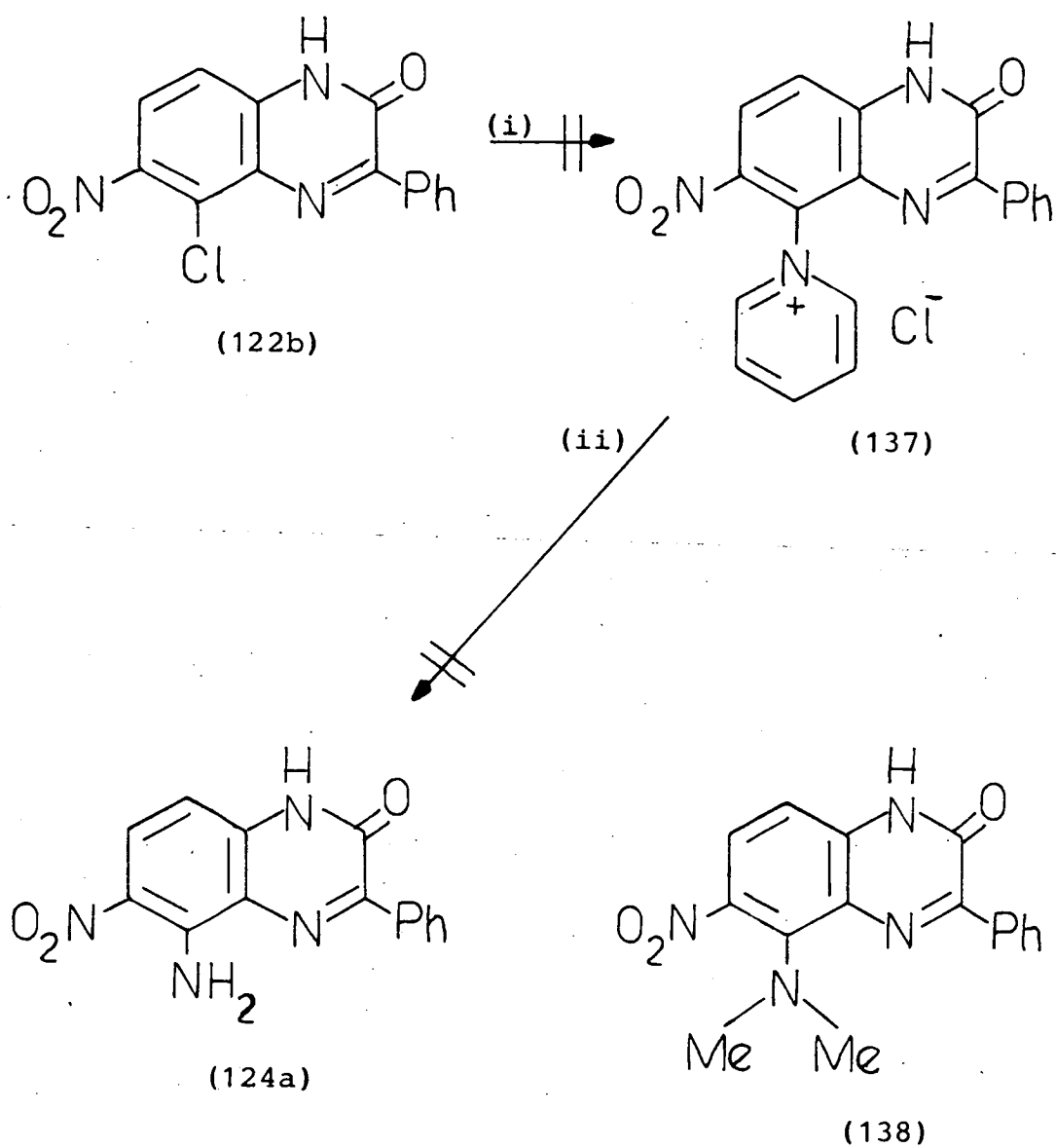
attempt (Scheme 25) was made to obtain the perchlorate salt of the nitroquinoxalinone N-oxide [(120b)→(133)] with a view to investigating its reaction with hydrochloric acid. It was considered that the perchlorate salt (133) might provide the 7-chloro-6-nitroquinoxalinone (121b) on treatment with hydrochloric acid. In practice however the only material isolated from the reaction of the quinoxalinone N-oxide (120b) with acetic anhydride and perchloric acid was a good yield of unreacted quinoxalinone N-oxide (120b). No product identifiable as the perchlorate salt (133) was obtained and thus the proposed investigation into the conversion of the latter into the 7-chloro-6-nitroquinoxalinone derivative (121b) was abandoned at this stage.

Having failed (Scheme 25) to induce the chlorination of the nitroquinoxalinone N-oxide (120b) to give the 7-chloro-6-nitroquinoxalinone (121b), attention was turned (Scheme 23) to the annulation of the 5-chloro-6-nitroquinoxalinone (122b). The reaction of the latter with amines could provide amino-nitroquinoxalinones (124), which in turn could give amino-acetonitrile derivatives (123). Base-catalysed cyclisation of the latter would then afford N-oxygenated imidazo[4,5-f]-quinoxalinone derivatives (125), interesting because of their potential biological properties. In practice reaction of the chloro-nitroquinoxalinone (122b) with liquid ammonia under sealed vessel conditions failed to give the expected amino-nitroquinoxalinone derivative (124a), the only product isolated being unreacted starting-material (122b).

Due to the failure of the direct amination of the chloro-nitroquinoxalinone (122b), alternative methods for the preparation

of the amino-nitroquinoxalinone (124a) were investigated. The reaction (Scheme 23) of the chloro-nitroquinoxalinone derivative (122b) with toluene-*p*-sulphonamide (tosyl amide) or diphenylphosphinamide¹⁵⁸ could provide the amino-nitroquinoxalinone derivatives (124b) or (124c) respectively. Hydrolysis of the latter would then give the primary amino-nitroquinoxalinone derivative (124a) required for further elaboration into *N*-oxygenated imidazoquinoxalinones (125).

However treatment of the 5-chloro-6-nitroquinoxalinone (122b) with tosyl amide in dimethylformamide did not give the expected tosylamino-quinoxalinone derivative (124b). The only products isolated from this reaction were the unreacted starting-materials. Thus the synthesis of the amino-quinoxalinone (124a) by hydrolysis of the tosylamino derivative (124b) could not be investigated. Reaction of the chloro-nitroquinoxalinone (122b) with the previously prepared diphenylphosphinamide [Scheme 13; (68)]¹⁵⁸ however, afforded a very low yield (5%) of solid which gave accurate mass data consistent with the molecular formula $C_{14}H_{10}N_4O_3$. The i.r. spectrum of the product showed broad NH/OH absorption at 3200-2700 cm^{-1} together with an amide carbonyl band at 1660 cm^{-1} , but did not contain any absorption due to an amino-substituent. The 1H n.m.r. spectrum contained two one-proton doublet resonances characteristic of H-7 and H-8 in the quinoxalinone ring system together with proton resonances due to a phenyl substituent. The observed spectroscopic features allowed the tentative formulation of this product as the 5-amino-6-nitroquinoxalinone (124a). However the very low yield of the product isolated prevented any definitive characterisation



(i) pyridine, Me_2NCHO , 50° , 24h and pyridine, Me_2NCHO , heat.
(ii) NH_3 .

Scheme 27

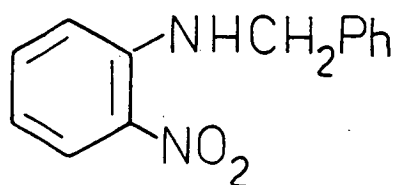
and the chemistry of the isolated compound was not further investigated.

In addition to the low yield of material tentatively formulated as the amino-nitroquinoxalinone (124a), good recoveries of unreacted 5-chloro-6-nitroquinoxalinone (122b) (78%) and diphenylphosphinamide (68) (83%) were also isolated from the reaction mixture on further work-up.

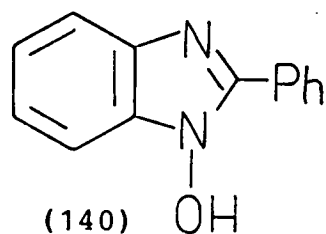
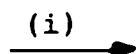
A further attempt (Scheme 27) was made to obtain the 5-amino-6-nitroquinoxalinone derivative (124a) via the pyridinium salt of the quinoxalinone (137). Treatment of the chloro-nitroquinoxalinone (122b) with pyridine could provide the pyridinium salt (137), thus activating the 5-position in the quinoxalinone ring to nucleophilic attack by ammonia to give the desired amino-nitroquinoxalinone derivative (124a). In practice reaction of the chloro-nitroquinoxalinone (122b) with pyridine in dimethylformamide at 50° afforded only unreacted quinoxalinone (122b). Heating the latter under reflux with pyridine in dimethylformamide also failed to give the pyridinium salt (137). The observed product was an orange-yellow solid which gave analytical data in accord with the molecular formula $C_{16}H_{14}N_4O_3$. The mass spectrum of this product did not show the expected parent ion at m/e 310, only an (M^++1) at m/e 311 was observed. The i.r. spectrum showed absorptions due to an NH/OH substituent and an amide carbonyl band at 3200-2600 and 1655 cm^{-1} respectively. The 1H n.m.r. spectrum of the product showed the aromatic proton resonances characteristic of a 5,6-disubstituted quinoxalinone derivative [e.g. (122b)] including the pair of doublets at δ 7.89 and 6.84 due to H-7 and H-8 respectively. The 1H n.m.r. spectrum of

the orange-yellow solid also contained a signal at $\delta 3.10$ which integrated for six protons and was assigned to an $N(CH_3)_2$ substituent. The observed analytical and spectroscopic details of the product allowed its formulation as the dimethylamino-nitroquinoxalinone derivative (138). The latter presumably arises from a pyridine-catalysed reaction of dimethylformamide with the chloro-nitroquinoxalinone derivative (122b).

Having failed (Schemes 23 and 27) to obtain an effective synthesis of the 5-amino-6-nitroquinoxalinone (124a) by a variety of methods, attention was turned to the preparation (Scheme 23) of the methylamino-quinoxalinone derivative (124d). The latter should be amenable to further elaboration to an aminoacetonitrile derivative (123d), base-catalysed cyclisation of which would give the N-oxygenated imidazo[4,5-f]quinoxalinone (125b). Thus, heating the chloro-nitroquinoxalinone (122b) in dimethylformamide with ethanolic methylamine at 50° afforded an orange solid in moderate yield (61%) which gave analytical and mass spectral data consistent with 5-methylamino-6-nitroquinoxalinone structure (124d). The i.r. spectrum of this product contained a broad NH band centered at 3250 cm^{-1} together with an absorption due to a carbonyl band at 1660 cm^{-1} . The ^1H n.m.r. spectrum of the product was also in accord with the methylamino-structure (124d), and in particular contained a doublet resonance at $\delta 4.2$ due to the methylamino substituent. The attempted reaction (Scheme 23) of the methylamino-nitroquinoxalinone (124d) with paraformaldehyde, potassium cyanide and zinc chloride in glacial acetic acid, as described (Scheme 12)^{154,155} for the synthesis of ortho-



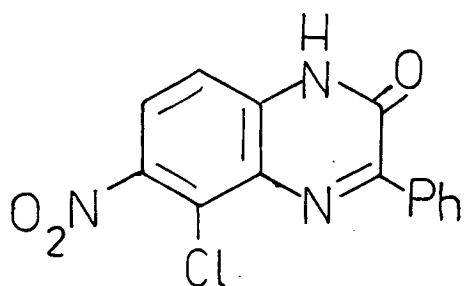
(139)



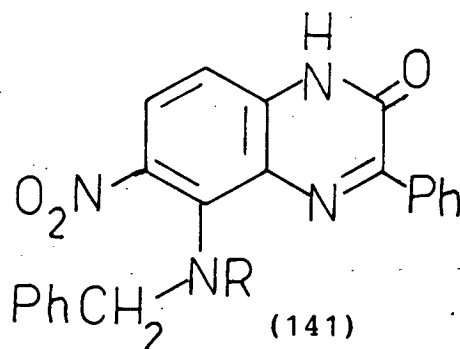
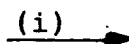
(140) OH

(i) NaOH, MeOH, heat.

Scheme 28

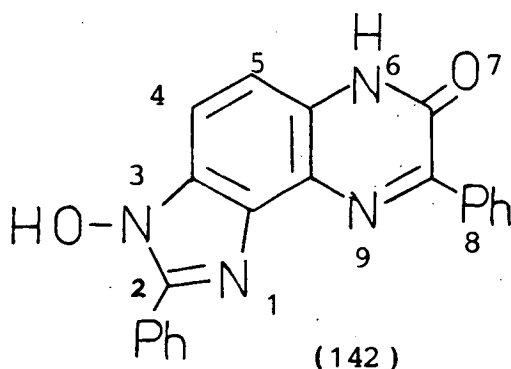
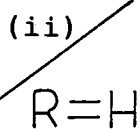


(122b)

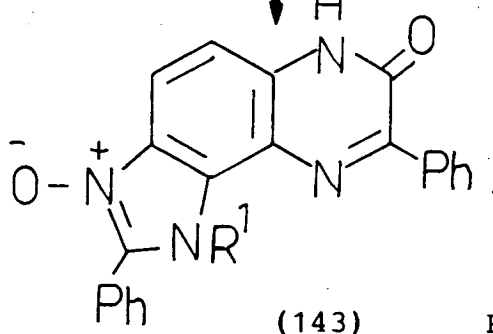
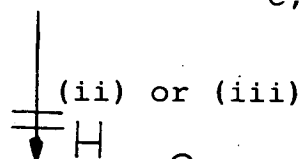


(141)

\underline{R}
a; H
b; Me
c; CH₂Ph



(142)



(143)

$\underline{R^1}$
a; Me
b; CH₂Ph

(i) PhCH₂NHR, Me₂NCHO, 50°.

(ii) NaOH, MeOH, heat.

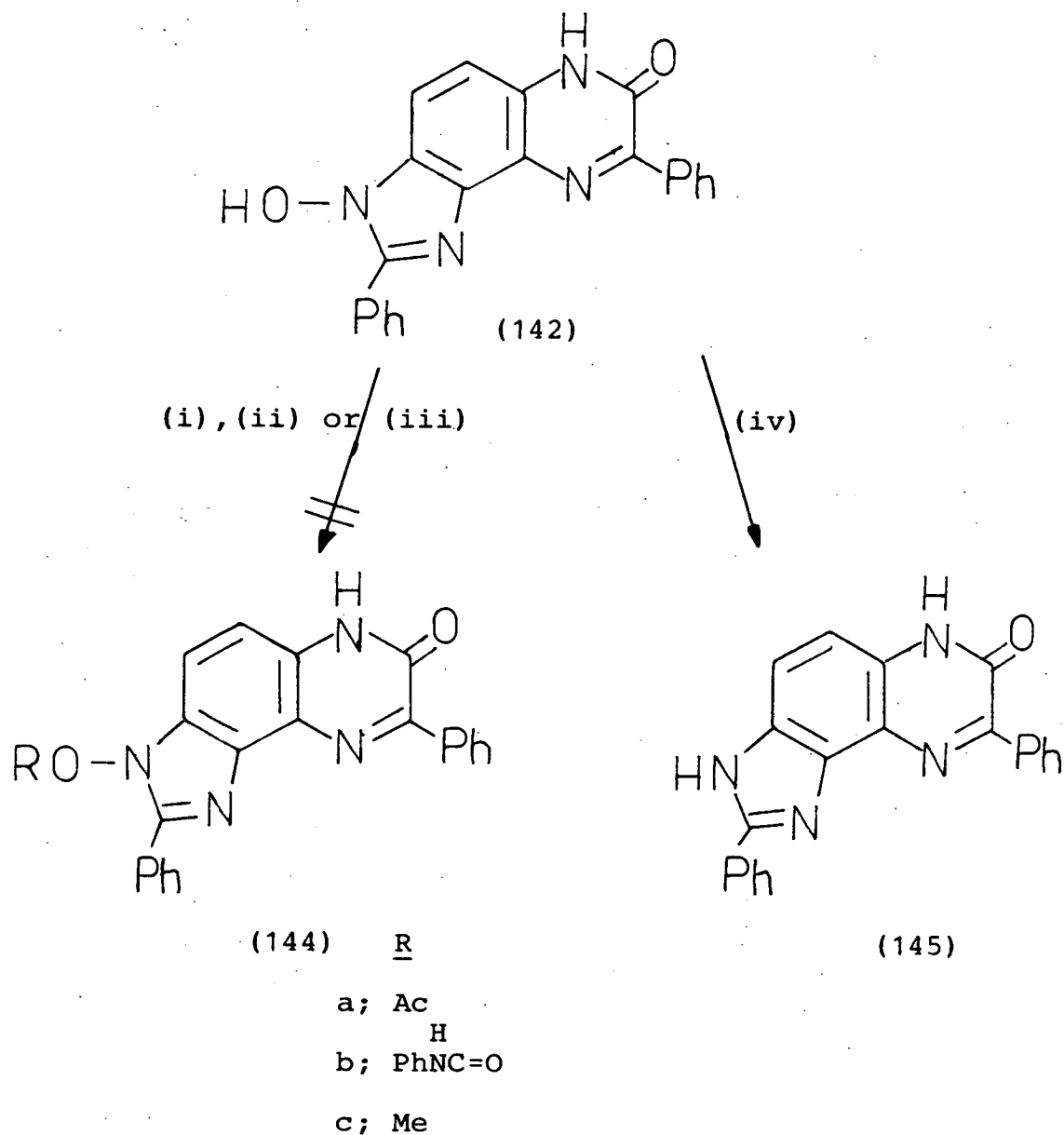
(iii) KOH, H₂O, pyridine, 100°.

Scheme 29

nitroanilinoacetonitrile derivatives (63), failed to give the methylaminoacetonitrile derivative (123d). The only product isolated from this reaction was a high yield of unreacted methylamino-quinoxalinone (124d). Due to the failure of this compound to react under the above conditions it was decided to abandon the synthesis of N-oxygenated imidazo[4,5-f]quinoxalines from amino-nitroquinoxalinones (124) as described in Scheme 23.

Base-catalysed cyclisations of N-substituted ortho-nitro-anilines containing an active methylene group in the side chain are known⁴³ to give N-oxygenated benzimidazoles. Reactions of this type are exemplified (Scheme 28)¹⁷⁰ by the reaction of the benzylamino derivative (139) with methanolic sodium hydroxide to give the benzimidazole N-oxide (140) which preferentially exists in the tautomeric N-hydroxybenzimidazole form. It was of interest (Scheme 29) to study the reaction of the chloro-nitroquinoxalinone derivative (122b) with benzylamine derivatives with a view to obtaining benzylamino-derivatives (141), base-catalysed cyclisation of which could give N-oxygenated imidazo[4,5-f]quinoxalinone derivatives (142) and (143).

In practice (Scheme 29) reaction of the 5-chloro-6-nitro-quinoxalinone (122b) with benzylamine in dimethylformamide afforded a moderate yield of a yellow solid which gave analytical and mass spectral data consistent with the molecular formula $C_{21}H_{16}N_4O_3$. The i.r. spectrum of the product contained carbonyl and nitro absorptions at 1660, 1500 and 1300 cm^{-1} , together with weak NH absorption at 3240 cm^{-1} . The 1H n.m.r. spectrum of the product at 64° showed resonances characteristic of an



- (i) Ac_2O , heat.
- (ii) $\text{PhN}=\text{C}=\text{O}$, Me_2NCHO , room temp., 24h.
- (iii) Me_2SO_4 , NaOH , H_2O .
- (iv) $\text{Na}_2\text{S}_2\text{O}_4$, H_2O , Me_2NCHO , heat.

NHCH_2 -substituent with a multiplet at $\delta 9.52$ - 9.34 and a doublet at $\delta 4.35$. There were also resonances due to twelve aromatic protons including two doublets at $\delta 8.21$ and 5.65 due to H-7 and H-8 of the quinoxalinone ring system. These assignments were further confirmed by a series of irradiation experiments in the ^1H n.m.r. spectrum. The observed analytical and spectroscopic properties allowed the formulation of the yellow solid product as the expected benzylamino-nitroquinoxalinone structure (141a).

Base-catalysed cyclisation of the benzylamino-nitroquinoxalinone (141a) with methanolic sodium hydroxide afforded a yellow solid which crystallised from glacial acetic acid-dimethylformamide to give 2,8-diphenyl-3-hydroxy-3H-imidazo[4,5-f]quinoxalin-7(6H)-one (142), which gave accurate mass data consistent with the assigned structure. The mass spectrum of the product also contained a fragment^{ion} at m/e 338 corresponding to deoxygenation of the compound. The i.r. spectrum showed broad NH/OH absorption centered at 3400 cm^{-1} , together with a carbonyl band at 1660 cm^{-1} . The ^1H n.m.r. spectrum was also consistent with the N-hydroxyimidazoquinoxalinone structure (142), the only unusual feature being that the expected doublet resonance for H-5 of the imidazoquinoxalinone (142) was hidden under a multiplet signal due to one of the phenyl-substituents.

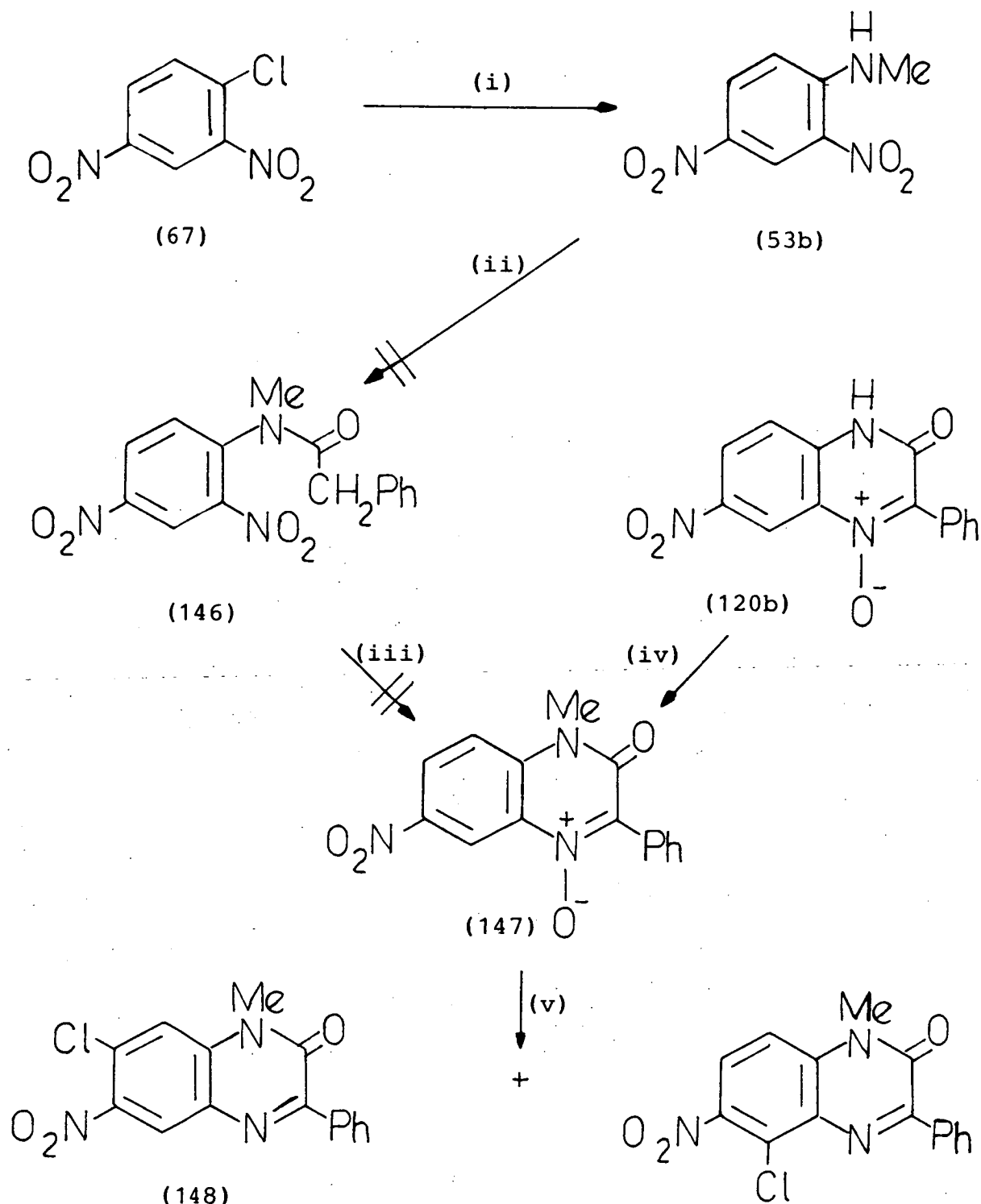
In an attempt to gain further evidence for the N-hydroxyimidazo[4,5-f]quinoxalinone structure (142), the synthesis (Scheme 30) of acetylated derivatives (144) were investigated. Heating the N-hydroxyimidazoquinoxalinone (142) with acetic anhydride afforded a good yield of a solid, tentatively

formulated as the 3-acetoxyimidazo[4,5-f]quinoxalinone (144a). The i.r. spectrum of this product contained carbonyl absorptions at 1810 and 1660 cm^{-1} suggesting the 3-acetoxy- structure (144a). However, the attempted crystallisation of this product for combustion analysis resulted in the degradation of the acetoxy-derivative (144a) to the N-hydroxyimidazo[4,5-f]quinoxalinone (142). Reaction of the latter with phenyl isocyanate in dimethylformamide failed to give any product identifiable as the expected imidazoquinoxalinone derivative (144b). The only product isolated from the reaction of the N-hydroxyimidazoquinoxalinone (142) with phenyl isocyanate was a complex mixture, which was not further investigated. The attempted methylation of the N-hydroxyimidazo[4,5-f]quinoxalinone derivative (142) was also unsuccessful. Treatment of the latter with dimethyl sulphate in aqueous sodium hydroxide gave only an intractable mixture and no product identifiable as the methylated imidazoquinoxalinone derivative (144c).

However (Scheme 30) reduction of the N-hydroxyimidazo[4,5-f]quinoxalinone (142) using sodium dithionate in aqueous dimethylformamide afforded an excellent yield of the imidazo[4,5-f]quinoxalinone (145), providing a convenient proof of structure for the N-hydroxyimidazoquinoxalinone derivative (142). The product isolated from reaction of the N-hydroxy-compound (142) with sodium dithionate in aqueous dimethylformamide gave accurate mass, i.r. and ^1H n.m.r. spectral data completely in accord with the reduced imidazo[4,5-f]quinoxalinone structure (145). In particular the ^1H n.m.r. spectrum showed two one-proton doublet resonances corresponding to H-4

and H-5 of the imidazoquinoxalinone structure (145) at δ 7.85 and 7.24 respectively.

The synthesis (Scheme 29) of the N-hydroxyimidazo-[4,5-f]quinoxalinone derivative (142) appears to be the first example of an N-oxygenated imidazoquinoxaline reported to date. A search of the literature provided no previous examples of this group of compounds, thus the synthesis of other N-oxygenated imidazo[4,5-f]quinoxalinone derivatives was investigated. Attempts were made (Scheme 29) to obtain substituted benzylamino-nitroquinoxalinone derivatives (141; R \neq H) with a view to obtaining imidazoquinoxalinone N-oxides (143). Reaction of the 5-chloro-6-nitroquinoxalinone (122b) with N-benzylmethylamine in dimethylformamide at 50° afforded a moderate yield (62%) of a yellow solid which gave analytical and spectroscopic properties in accord with the N-benzyl-N-methylaminoquinoxalinone structure (141b). In particular the ¹H n.m.r. spectrum of the product contained signals due to a methylene and an N-methyl substituent at δ 4.59 and 2.88 respectively. Unfortunately the attempted base-catalysed cyclisation of the N-benzyl-N-methylaminoquinoxalinone derivative (141b) failed to give the expected imidazo[4,5-f]quinoxalinone N-oxide derivative (143a). Heating a solution of the N-benzyl-N-methylaminoquinoxalinone (141b) in pyridine with aqueous potassium hydroxide at 100° afforded only a high yield of unreacted starting-material (141b). Similarly heating a solution of the quinoxalinone (141b) in methanolic sodium hydroxide also gave only unreacted N-benzyl-N-methylaminoquinoxalinone (141b), with no product identifiable as the imidazo[4,5-f]quinoxalinone N-oxide (143a). The failure of



- (i) MeNH₂, EtOH, heat.
- (ii) PhCH₂COCl, C₆H₆, heat and PhCH₂COCl, NaH, Me₂NCHO.
- (iii) base.
- (iv) Me₂SO₄, K₂CO₃, Me₂C=O, heat.
- (v) AcCl, AcOH, heat or MeC₆H₄SO₂Cl, Me₂NCHO, 100°.

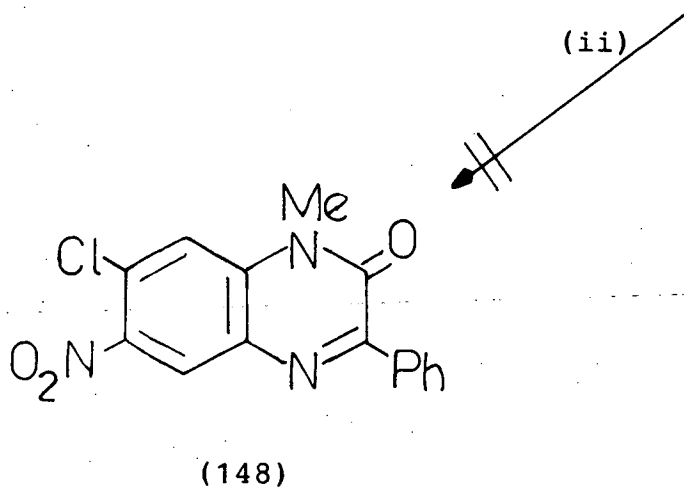
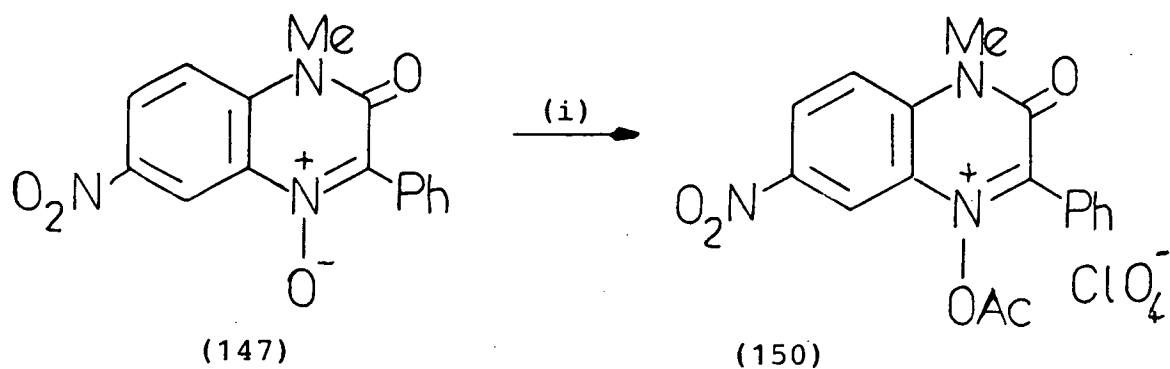
this base-catalysed cyclisation reaction was unexpected and could possibly be attributed to the instability of the N-oxide product (143a).

An attempt (Scheme 29) was made to obtain the N,N-dibenzylamino-nitroquinoxalinone derivative (141c), with a view to studying its base-catalysed cyclisation to the imidazoquinoxalinone N-oxide (143b). However reaction of the chloro-nitroquinoxalinone (122b) with dibenzylamine in dimethylformamide at 50° failed to give the dibenzylaminoquinoxaline (141c). The only products isolated from the reaction mixture were an intractable solid and a complex multicomponent oil, which were not further investigated. The failure of this reaction, which was thought to be due to a steric effect, precluded any investigation into the base-catalysed cyclisation of the dibenzylamino-derivative (141c) to the imidazo[4,5-f]-quinoxalinone N-oxide (143b).

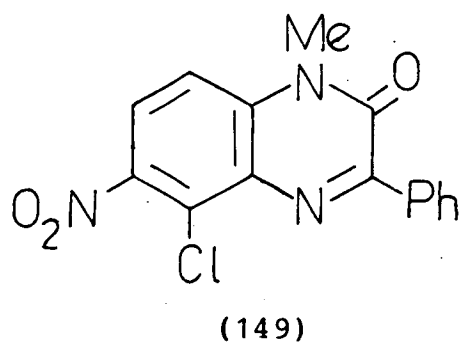
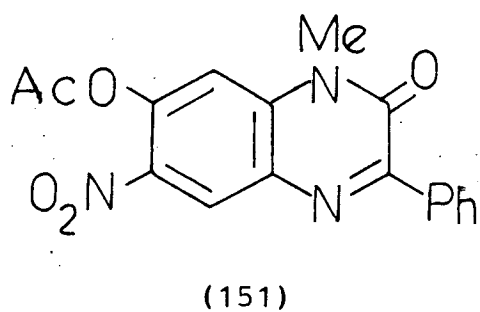
Having failed to effect the synthesis (Scheme 29) of imidazoquinoxalinone N-oxides (143) attention was turned to the preparation (Scheme 31) of chloro-N-methyl-nitroquinoxalinones (148) and/or (149) suitable for further elaboration to N-oxygenated imidazoquinoxalinones. The synthesis (Scheme 23) of chloroquinoxalinone derivatives (121a) and (122b), by reaction of the latter with acetyl chloride in glacial acetic acid, has been discussed previously (see page 198). Therefore, the approach adopted (Scheme 31) for the preparation of the chloro-nitroquinoxalinone derivatives (148) and/or (149) involved the synthesis and subsequent chlorination of the N-methylquinoxalinone N-oxide (147). The preparation of the N-oxide (147) was approached using two different synthetic

strategies. First, the attempted synthesis and subsequent base-catalysed cyclisation of the 2,4-dinitrophenylacetamide (146), then the methylation of the previously prepared quinoxalinone N-oxide (120b).

In practice the attempted acetylation of the previously prepared 2,4-dinitro-N-methylaniline (53b)¹⁵⁶ failed to give the N-methylacetamide derivative (146) required for base-catalysed cyclisation to the N-methylquinoxalinone N-oxide (147). Heating 2,4-dinitro-N-methylaniline (53b) with phenylacetyl chloride in benzene afforded only unreacted starting-material (53b). Similarly, the attempted sodium hydride catalysed reaction of the latter with phenylacetyl chloride also gave only unreacted 2,4-dinitro-N-methylaniline (53b). However the required N-methylquinoxalinone N-oxide (147) was readily prepared¹⁶⁶ by methylation of the quinoxalinone N-oxide derivative (120b). Heating the latter with dimethyl sulphate in acetone in the presence of potassium carbonate afforded a good yield of the N-methylquinoxalinone N-oxide (147).¹⁶⁶ Reaction of the quinoxalinone N-oxide derivative (147) with acetyl chloride in glacial acetic acid gave a moderate yield of a solid (54%) whose ¹H n.m.r. spectrum suggested it to be a mixture of the 7-chloro-6-nitroquinoxalinone (148) and the 5-chloro-6-nitroquinoxalinone (149). In particular the ¹H n.m.r. spectrum contained two one-proton doublet resonances at δ 8.18 and 7.64 assignable to H-7 and H-8 of the 5-chloro-6-nitroquinoxalinone derivative (149) together with two one-proton singlet resonances at δ 8.44 and 7.82 assignable to H-5 and H-8 of the 7-chloro-6-nitroquinoxalinone derivative (148) respectively. T.l.c. of the solid



OR



(i) Ac_2O , HClO_4 , AcOH .

(ii) HCl .

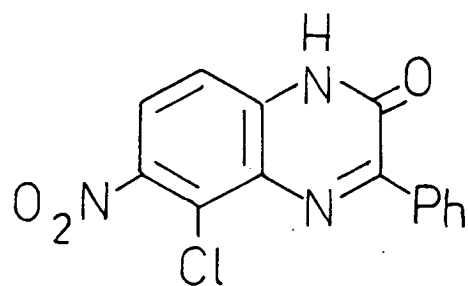
mixture indicated that the isomeric quinoxalinones (148) and (149) would not be resolvable on a preparative scale.

Due to the complicating formation of an unresolvable mixture of the two chloro-nitroquinoxalinone isomers (148) and (149) on treating the N-methylquinoxalinone N-oxide (147) with acetyl chloride in glacial acetic acid, alternative routes for the synthesis of one or other of the isomers (148) and (149) were investigated. Thus, (Scheme 31) heating the quinoxalinone N-oxide (147) with toluene-p-sulphonyl chloride (tosylchloride) in dimethylformamide might provide the 7-chloro-6-nitroquinoxalinone (148). The mechanism (Schemes 24 and 25) postulated for the formation of chloro-nitroquinoxalinone derivatives involves the formation of an intermediate adduct e.g. [Scheme 25; (132)]. It was anticipated that in the reaction (Scheme 31) of the N-methylquinoxalinone (147) with tosyl chloride an analogous intermediate would be formed initially, which might react preferentially with chloride ion to give the 7-chloro-6-nitroquinoxaline (148). The alternative 5-chloro-derivative (149) was considered less likely due to steric hindrance at the C-5 position in the N-oxygenated quinoxalinone intermediate. In practice reaction of the N-methylquinoxalinone N-oxide (147) with tosyl chloride in dimethylformamide gave only a moderate recovery of unreacted starting-material (147) and a complex multicomponent gum.

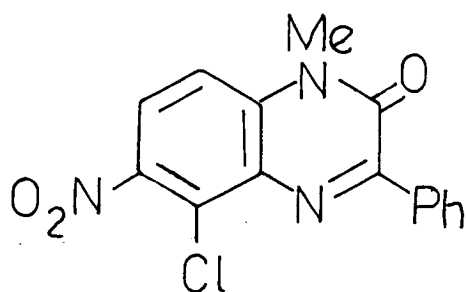
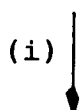
The synthesis (Scheme 26) ¹⁶⁹ of chloroquinoxalinone derivatives (136) from perchlorate salts (135) has already been discussed. Preparation (Scheme 32) of the N-methylquinoxalinone-perchlorate salt (150) could provide a possible

route to the chloroquinoxalinone derivatives (148) and (149) via treatment with hydrochloric acid. In practice treatment of the N-methylquinoxalinone N-oxide (147) with acetic anhydride in glacial acetic acid followed by dropwise addition of aqueous perchloric acid in acetic anhydride afforded a good yield of a solid which was tentatively formulated as the perchlorate salt (150). The i.r. spectrum of the product contained a carbonyl band at 1715 cm^{-1} , consistent with the proposed structure (150). Perchlorate salts of this type are known¹⁶⁹ to be unstable and the product was immediately reacted with concentrated hydrochloric acid. However the only product isolated from this reaction was a quantitative yield of the N-methylquinoxalinone N-oxide (147), presumably from acid hydrolysis of the perchlorate salt (150).

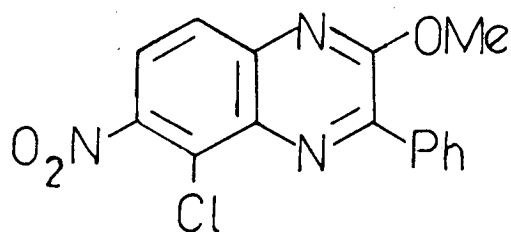
Work up of the acetic anhydride-acetic acid mother liquor from the above reaction afforded a brown crystalline solid. The analytical and mass spectral data for the product were consistent with the molecular formula $\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}_5$. The i.r. spectrum of the product contained carbonyl bands at 1770 and 1670 cm^{-1} together with nitro-absorption at 1515 and 1340 cm^{-1} . The ^1H n.m.r. spectrum showed two singlets, one-proton resonances at $\delta 8.61$ and 7.71 and signals due to a phenyl, an N-methyl and a methyl substituent at $\delta 8.27\text{--}8.22$, $7.56\text{--}7.52$, 3.31 and 2.41 . The observed analytical and spectroscopic data allowed the formulation of this product as 7-acetoxy-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (151). The acetoxy derivative (151) was thought to arise from reaction of the perchlorate salt (150) with acetate present in the reaction mixture.



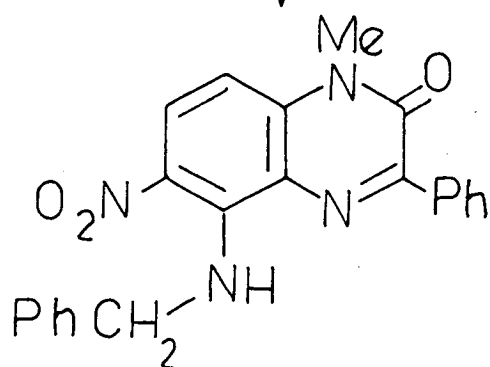
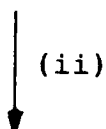
(122b)



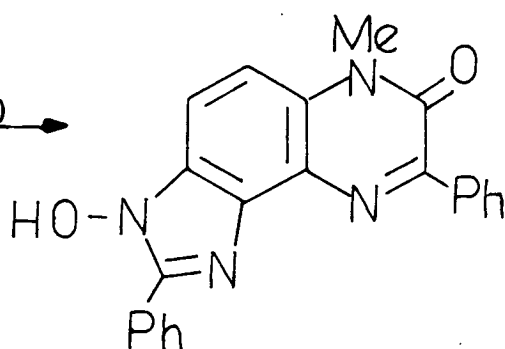
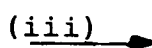
(149)



(152)



(153)



(154)

(i) Me_2SO_4 , K_2CO_3 , $\text{Me}_2\text{C}=\text{O}$, heat or Me_2SO_4 , NaOH , H_2O ,
or MeI , NaH , Me_2NCHO .

(ii) PhCH_2NH_2 , Me_2NCHO , 50° .

(iii) KOH , H_2O , pyridine 100° or NaOH , MeOH , heat.

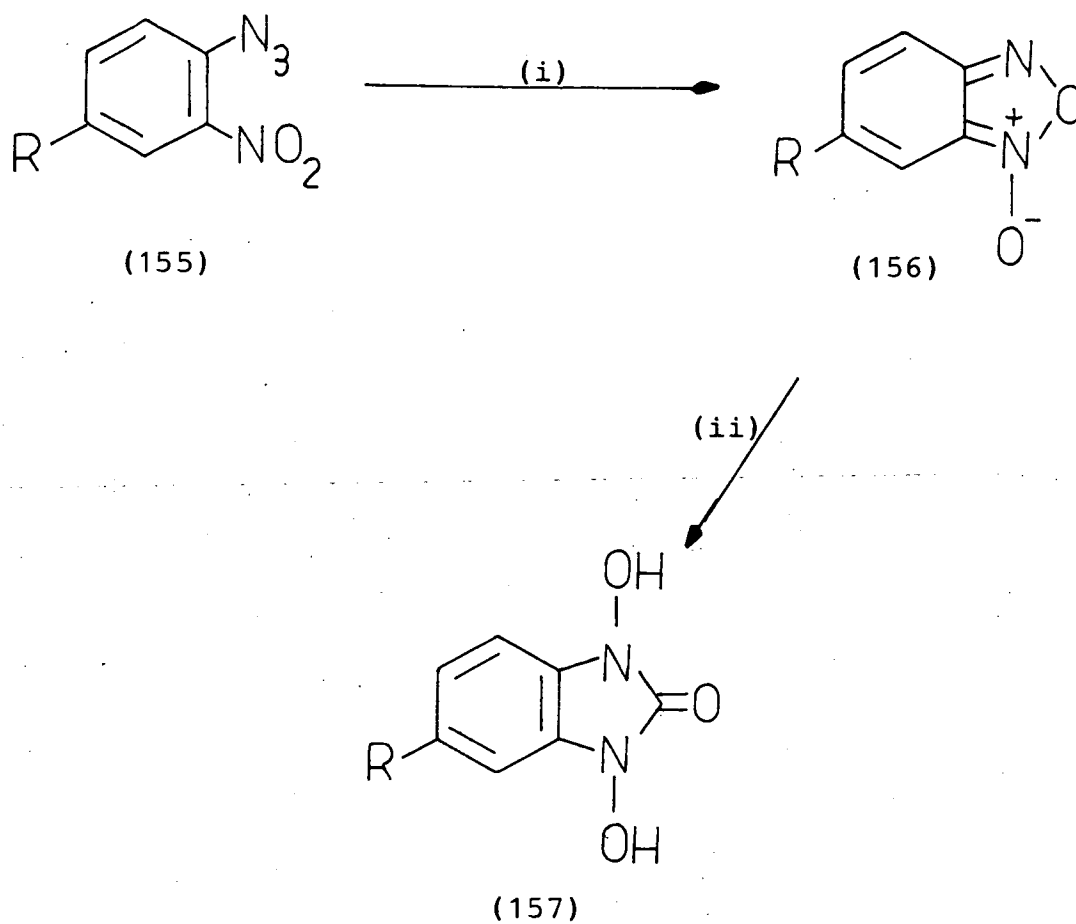
Methylation (Scheme 33) of the 5-chloro-6-nitroquinoxalinone derivative (122b) prepared previously, could provide a synthesis of the N-methyl analogue (149). Reaction of the latter with benzylamine and subsequent base-catalysed cyclisation of the resulting amino-nitroquinoxalinone (153) might give an N-oxygenated imidazo[4,5-f]quinoxalinone derivative (154). Heating a suspension of the chloro-nitroquinoxalinone (122b) with dimethyl sulphate in acetone in the presence of potassium carbonate afforded a low yield of yellow solid which gave analytical and mass spectral data in accord with the expected 5-chloro-1-N-methyl-6-nitroquinoxalinone structure (149). The spectroscopic properties of the product were also consistent with the quinoxalinone structure (149). The i.r. spectrum of the product contained absorptions due to a carbonyl and nitro substituents at 1665, 1530 and 1345 cm^{-1} . The ^1H n.m.r. spectrum contained the two one-proton doublet resonances at δ 8.18 and 7.65, characteristic of the 5,6-disubstituted quinoxaline ring system, as well as a signal at δ 3.70 assignable to an N-methyl substituent.

Further work-up of the methylation reaction mixture afforded a very low yield (0.5%) of a second yellow solid whose analytical and mass spectral data were also consistent with a methylated quinoxalinone derivative. The i.r. spectrum of this product contained bands due to a nitro group at 1565 and 1365 cm^{-1} but lacked absorption due to a carbonyl substituent. The ^1H n.m.r. spectrum indicated the presence of the quinoxalinone ring system displaying the usual proton resonances together with a signal at δ 4.19, which integrated for three protons. These spectroscopic features allowed the

formulation of this product as the 2-methoxy isomer of the quinoxalinone derivative (152). The isolation of the 2-methoxyquinoxalinone (152) indicates that the chloro-nitroquinoxalinone (122b) can exist as the tautomeric 2-hydroxyquinoxalinone isomer under basic conditions.

Two attempts were made to try and improve the yield of the N-methyl-chloroquinoxalinone (149) by using alternative conditions for the methylation of the chloro-nitroquinoxalinone (122b). Reaction of this compound with dimethyl sulphate in aqueous sodium hydroxide afforded a slightly improved yield of the methylated derivative (149) together with some unreacted chloro-nitroquinoxalinone (122b). However reaction of the sodium salt of the chloro-nitroquinoxalinone (122b), preformed using sodium hydride in dimethylformamide, with methyl iodide gave a better yield of the product (149) and thus was the method of choice for the preparation of the N-methylated derivative (149).

Reaction of the 5-chloro-1-N-methyl-6-nitroquinoxalinone (149) with benzylamine in dimethylformamide at 50° afforded a good yield (82%) of an orange-yellow solid whose analytical and mass spectral data were consistent with the molecular formula $C_{22}H_{18}N_4O_3$. The i.r. spectrum of this product contained bands characteristic of an NH, a carbonyl and a nitro substituent. The 1H n.m.r. spectrum contained the two one-proton doublet resonances characteristic of H-7 and H-8 of the quinoxalinone ring system, together with those resonances characteristic of two phenyl substituents. A broad signal at $\delta 9.40$ and a two-proton doublet at $\delta 5.40$ indicated the presence of an $\underline{NHCH_2}$ substituent and a singlet resonance at



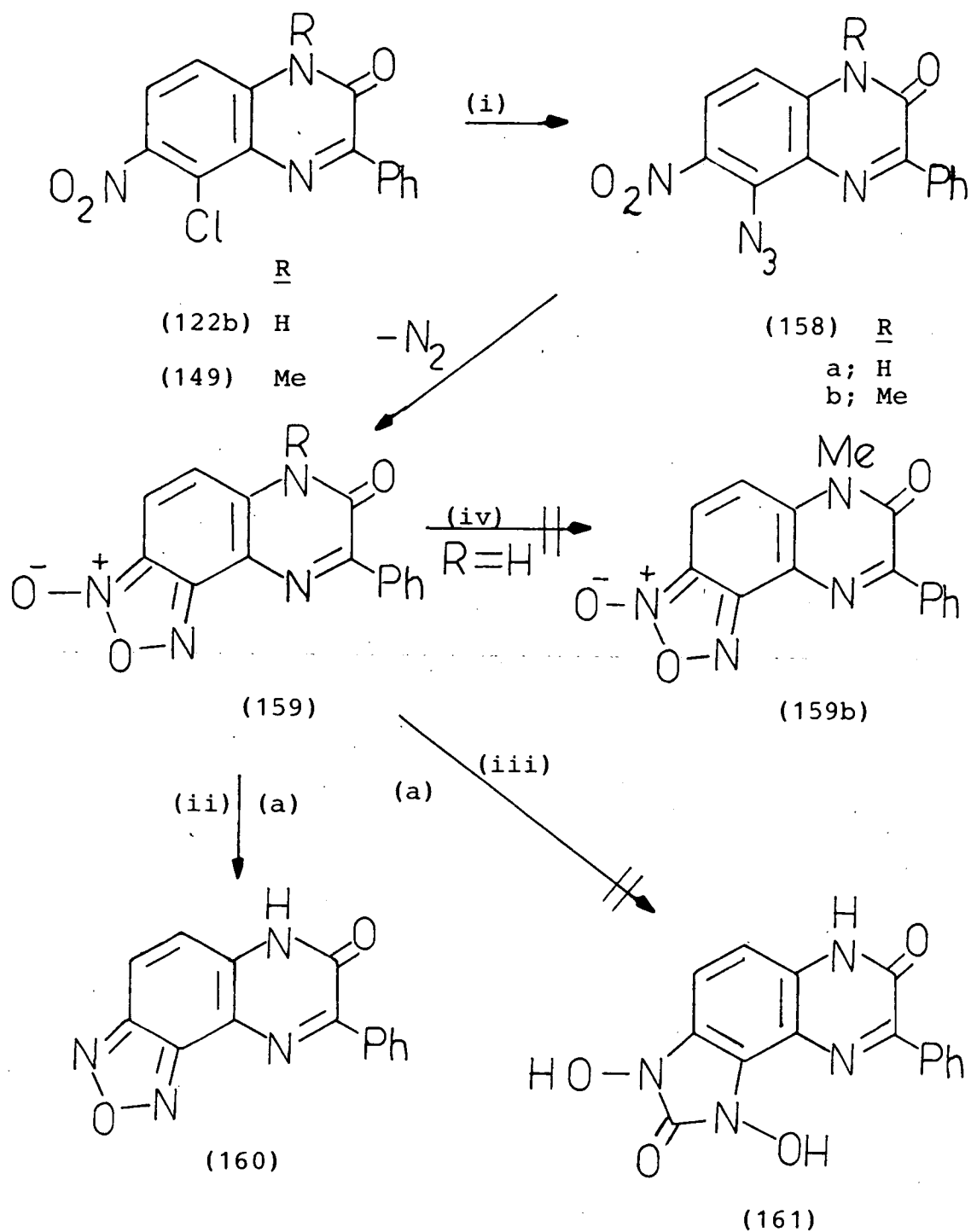
(i) heat or hv.

(ii) H_2CO , KOH, MeOH, H_2O , 40-50°.

Scheme 34

δ 3.80 was assigned to an N-methyl moiety. The observed analytical and spectroscopic data were consistent with the benzylamino-nitroquinoxalinone structure (153). The attempted base-catalysed cyclisation of the latter using methanolic sodium hydroxide under conditions successfully employed for the cyclisation (Scheme 29) of the amino-nitroquinoxalinone (141a) to the N-hydroxyimidazo[4,5-f]quinoxalinone (142), failed to give the expected (Scheme 33) N-oxygenated imidazoquinoxalinone (154). Under these conditions the only product isolated was unreacted benzylamino N-methyl-nitroquinoxalinone (153). However, treatment of the latter with aqueous potassium hydroxide in pyridine afforded an excellent yield (91%) of a yellow solid which gave accurate mass data consistent with the N-hydroxy-N-methyylimidazo[4,5-f]quinoxalinone structure (154). The mass spectrum of this product contained a fragment at m/e 352 corresponding to deoxygenation of the N-oxygenated imidazoquinoxalinone (154), providing further evidence for the proposed structure. The i.r. and ^1H n.m.r. spectroscopic details of the product were also consistent with the N-hydroxy-N-methyylimidazoquinoxalinone structure (154). The base-catalysed cyclisation of the benzylamino-N-methyl-nitroquinoxalinone (153) to the N-hydroxy-N-methyylimidazo[4,5-f]quinoxalinone (154) provides the second example of novel N-oxygenated imidazoquinoxalines to complement the previously prepared N-oxygenated imidazoquinoxalinone [Scheme 29; (142)].

The synthesis of benzofuroxan derivatives by thermolysis or photolysis of ortho-nitroarylazides is well known⁴³ and is exemplified (Scheme 34)¹⁷¹ by the pyrolysis of the ortho-



- (i) NaN_3 , H_2O , Me_2NCHO , heat.
- (ii) $\text{Na}_2\text{S}_2\text{O}_4$, NaOH , H_2O .
- (iii) H_2CO , KOH , MeOH , H_2O , $40-50^\circ$.
- (iv) Me_2SO_4 , K_2SO_3 , Me_2CO , heat or Me_2SO_4 , NaOH , H_2O .

nitroarylazide (155; R=H) to the benzofuroxan (156; R=H) in high yield. The subsequent preparation of 1,3-di-N-hydroxybenzimidazolones (157)¹⁶¹ from benzofuroxan derivatives (156) on treatment of the latter with formaldehyde under base-catalysed conditions has been discussed previously. An analogous approach was employed in investigations (Scheme 35) into the synthesis of oxadiazolo[3,4-f]quinoxalinone N-oxides (159) and their subsequent elaboration to the novel di-N-hydroxyimidazoquinoxalinones (161), which are of interest in view of their potential biological activity.

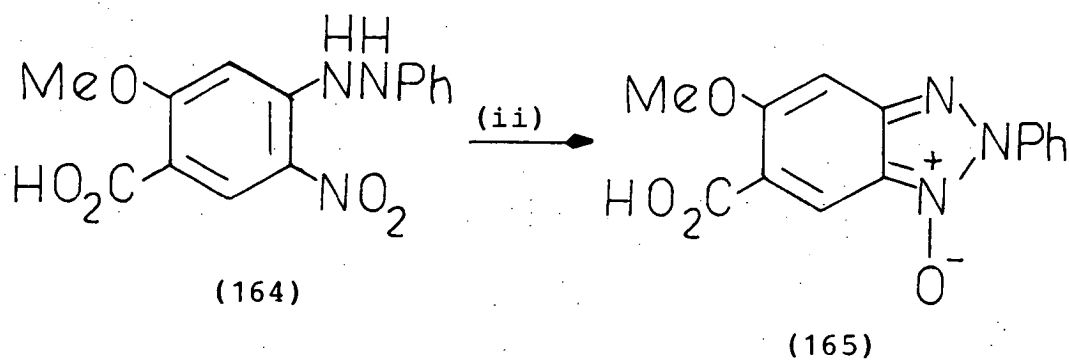
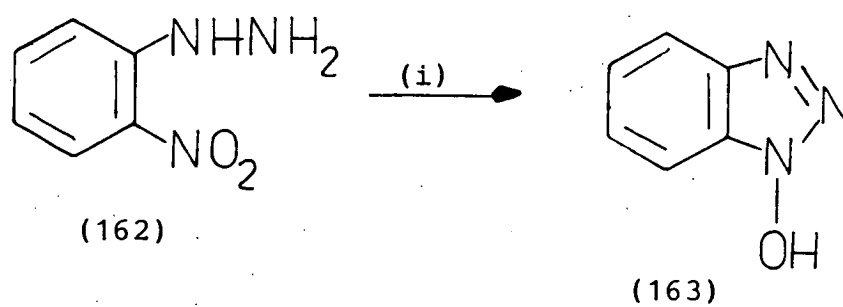
In practice heating the chloro-nitroquinoxalinone (122b) with sodium azide in aqueous dimethylformamide afforded a moderate yield (52%) of a yellow-brown solid which gave analytical and mass spectral data consistent with the molecular formula $C_{14}H_8N_4O_3$. The mass spectrum of the product also contained a fragment at m/e 264 corresponding to loss of oxygen from the parent ion at m/e 280. The i.r. spectrum contained broad absorption due to an NH/OH substituent at $3200-2700\text{ cm}^{-1}$ and a carbonyl band at 1660 cm^{-1} . The 1H n.m.r. spectrum contained only aromatic proton resonances including the two one-proton doublet resonances at $\delta 7.66$ and 7.29 corresponding to H-7 and H-8 of a quinoxalinone ring system. The observed analytical and spectroscopic properties allowed the formulation of this product as the oxadiazolo-[3,4-f]quinoxalinone N-oxide structure (159a). Further evidence for this structure was obtained by reduction of the compound, with sodium dithionite in aqueous sodium hydroxide, to the oxadiazoloquinoxalinone (160). The observed accurate mass and spectroscopic properties for the oxadiazoloquinox-

alinone (160) were in accord with the proposed structure.

Unfortunately the attempted reaction of the oxadiazolo-[3,4-f]quinoxalinone N-oxide (159a) with formaldehyde under base-catalysed conditions did not give the expected di-N-hydroxyimidazoquinoxalinone (161). The only product isolated from the reaction of the oxadiazoloquinoxalinone N-oxide (159a) with formaldehyde in the presence of aqueous methanolic potassium hydroxide was a quantitative yield of unreacted starting-material (159a).

The reaction of the chloro-N-methylquinoxalinone (149) with sodium azide in aqueous dimethylformamide failed to give the expected oxadiazoloquinoxalinone N-oxide (159b). The observed products from this reaction were a series of multi-component solids and gums which yielded no material identifiable as the oxadiazoloquinoxalinone N-oxide (159b). The alternative approach to the N-methyloxadiazoloquinoxalinone N-oxide (159b) via methylation of the available oxadiazoloquinoxalinone (159a) also failed to give the desired N-methylated derivative (159b). Heating the oxadiazoloquinoxalinone (159a) with dimethyl sulphate in acetone in the presence of potassium carbonate gave only a good recovery of the unreacted starting-material (159a). The attempted methylation of the latter using dimethyl sulphate in aqueous sodium hydroxide afforded only complex solid mixtures which were not further investigated.

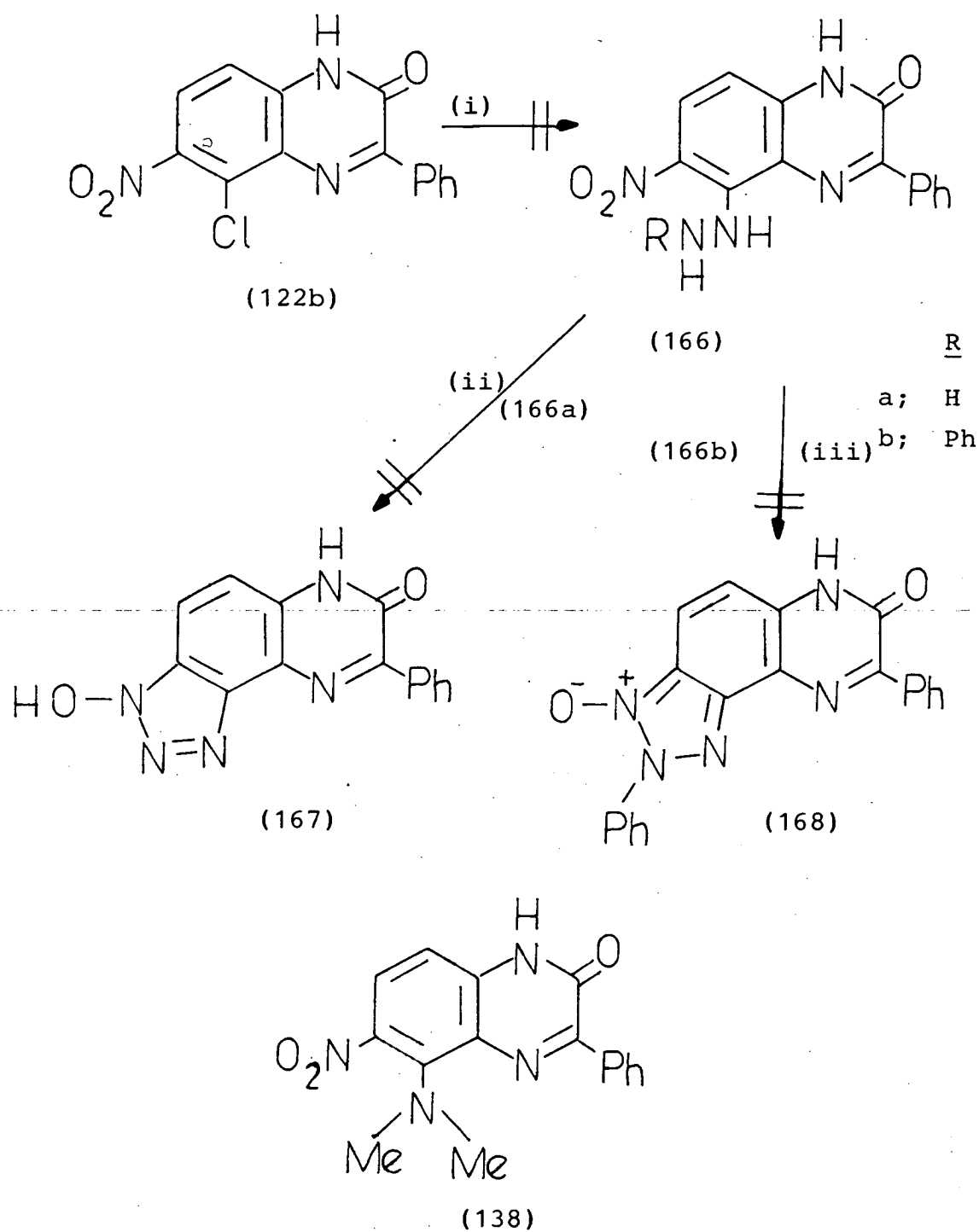
The oxadiazolo[3,4-f]quinoxalinone N-oxide (159a) prepared by reaction of the chloro-nitroquinoxalinone (122b) with sodium azide presumably arises by the intermediate formation and spontaneous cyclisation of the nitroquinoxalinone-azide derivative (158a). The failure to obtain the analogous



(i) NaOH, H₂O, heat.

(ii) MeCO₂H, heat.

Scheme 36



(i) RNHNH_2 , Me_2NCHO , heat.

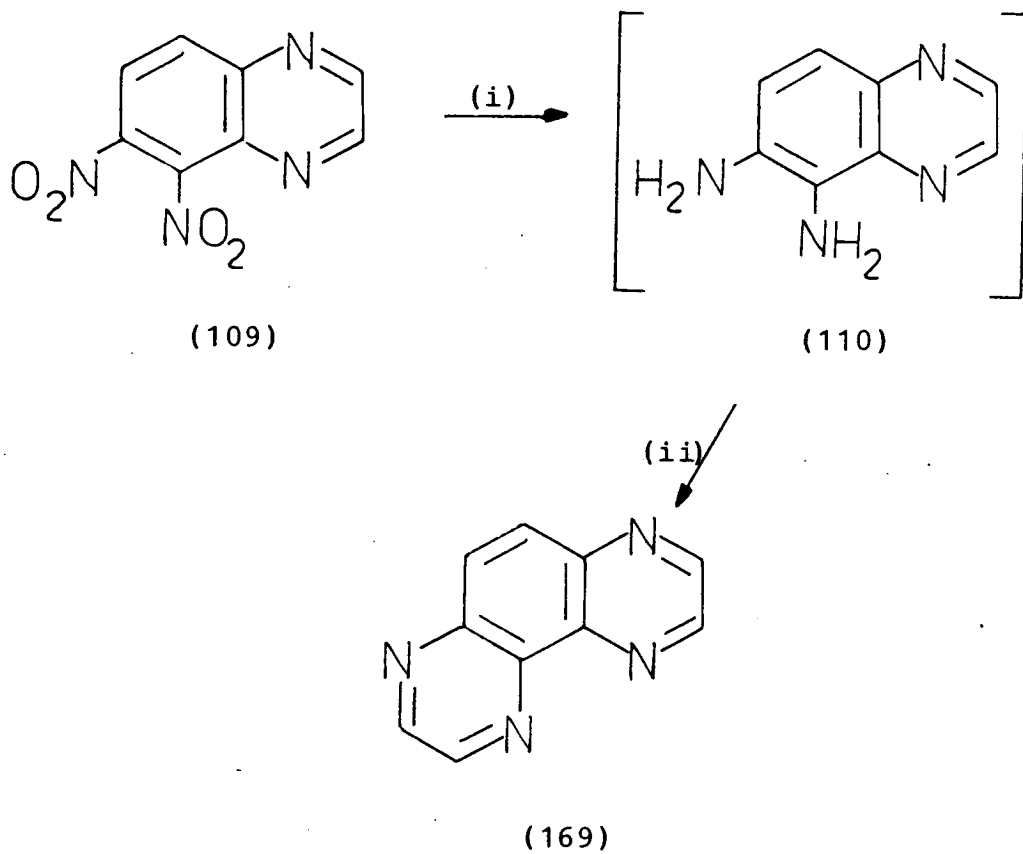
(ii) base.

(iii) MeCO_2H , heat or base.

N-methyloxidiazolo[3,4-f]quinoxalinone N-oxide (159b) on reaction of the chloro-N-methylquinoxalinone (149) with sodium azide can be attributed to difficulties in forming a quinoxalinone-azide derivative (158b).

Base-catalysed cyclisations of ortho-nitrophenylhydrazines are known⁴³ to give 1-hydroxybenzotriazoles. Reactions of this type are exemplified (Scheme 36)¹⁷² by the aqueous sodium hydroxide catalysed cyclisation of the phenylhydrazine (162) to 1-hydroxybenzotriazole (163). Cyclisation of N-substituted ortho-nitroarylhydrazines e.g. (164) are also known¹⁷³ to give benzotriazole N-oxides e.g. (165). Therefore it was of interest (Scheme 37) to investigate the synthesis of nitroquinoxalinone-hydrazines (166) with a view to studying their base-catalysed cyclisation to N-oxygenated triazoloquinoxalinones (167) and (168). Tricyclic ring systems of this type are isosteric with 'stretched' aza-purines and thus might have useful biological activity. The reaction of the 5-chloro-6-nitroquinoxalinone (122b) with hydrazine derivatives was attempted, with a view to obtaining the required quinoxalinone-hydrazine derivatives (166) for subsequent elaboration into N-oxygenated triazoloquinoxalinones (167) and (168).

Heating the chloro-nitroquinoxalinone (122b) with hydrazine monohydrate in dimethylformamide did not give the expected hydrazine derivative (166a). The only product isolated from this reaction was shown to be the N,N-dimethyl-amino-nitroquinoxalinone (138), by comparison with an authentic sample prepared previously (see Scheme 27). Heating the chloro-nitroquinoxalinone (122b) with phenylhydrazine in dimethylformamide at 50° also failed to give the expected



(i) SnCl_2 , HCl , H_2O , 50° .

(ii) Sodium glyoxal bisulphate, H_2O , heat.

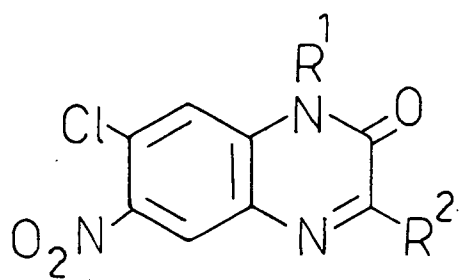
Scheme 38

quinoxalinone-hydrazine derivative (166b). The only product isolated from this reaction was a high yield of unreacted starting-material (122b). Reaction of chloro-nitroquinoxalinone (122b) with phenylhydrazine in dimethylformamide under harsher conditions also failed to give the quinoxalinone-hydrazine derivative (166b). Heating the quinoxalinone (122b) under reflux with phenylhydrazine in dimethylformamide gave a brown gum which could not be further resolved.

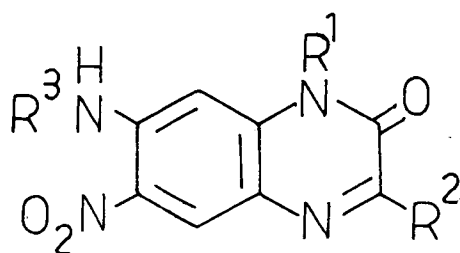
The failure of the chloro-nitroquinoxalinone (122b) to react with hydrazine derivatives prevented the proposed investigation into the preparation of N-oxygenated triazoloquinoxalinones (167) and (168) as outlined in Scheme 37. The formation of the N,N-dimethylaminoquinoxalinone (138) on reaction of the chloro-nitroquinoxalinone (122b) with hydrazine monohydrate can be explained in terms of a hydrazine catalysed reaction of the quinoxalinone (122b) with dimethylformamide used as solvent in the reaction mixture.

(iv) New Synthetic Approaches to N-Oxygenated 'Stretched' Pteridine Azalogues Based on Annulation Reactions of Nitroquinoxaline Derivatives

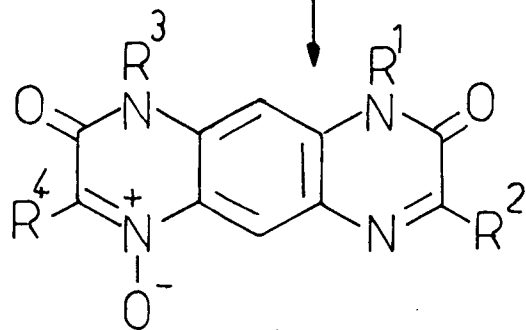
In view of the biological properties of prox-benzo-pteridine derivatives the synthesis of the isosteric pyrazinoquinoxalines and their N-oxygenated derivatives were investigated. The synthesis of pyrazinoquinoxalines have been reported in the literature and are exemplified (Scheme 38)¹⁷⁴ by reduction of the dinitroquinoxaline derivative (109), which reacted in situ via a diaminoquinoxaline intermediate (110),



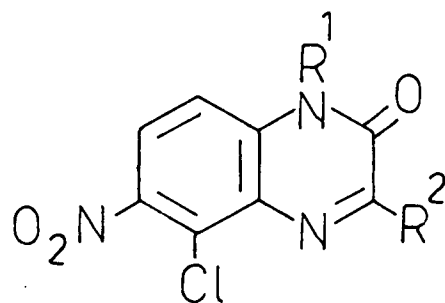
(112)



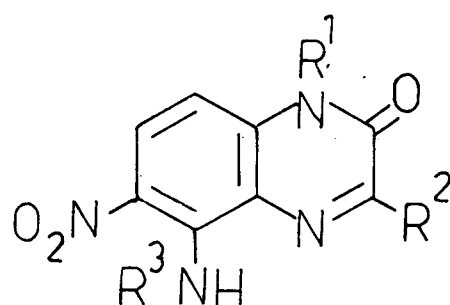
(170)



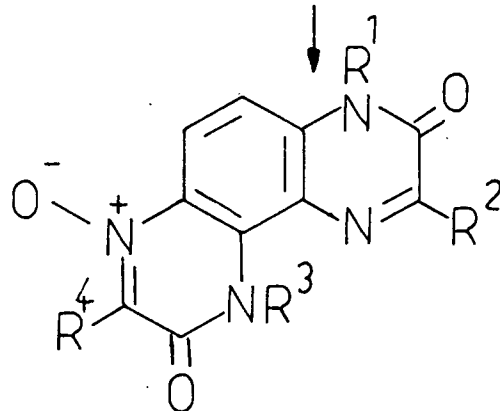
(172)



(113)

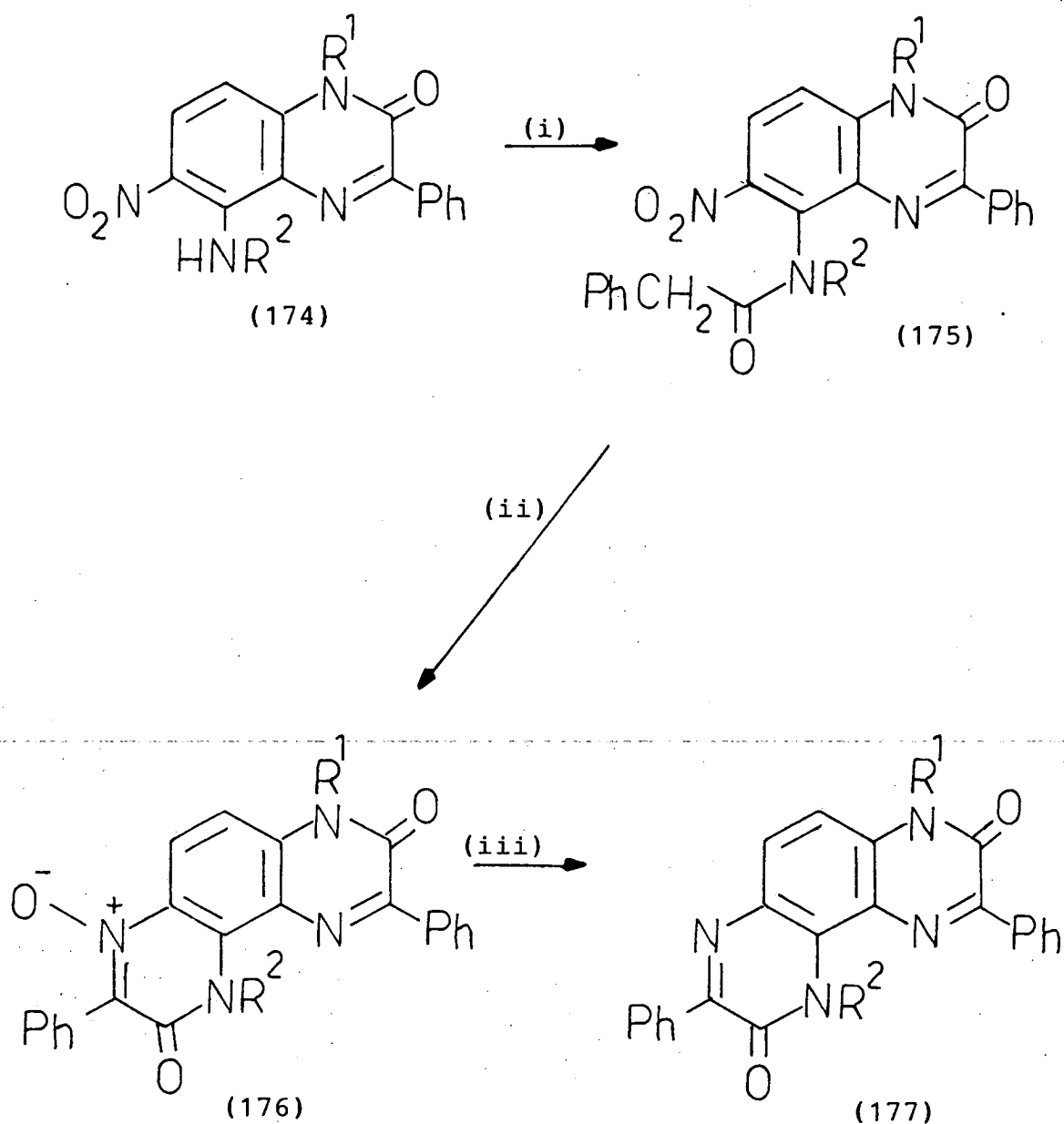


(171)



(173)

Scheme 39



	<u>R¹</u>	<u>R²</u>
a;	H	Me
b;	Me	Me
c;	H	CH ₂ Ph
d;	Me	CH ₂ Ph

- (i) PhCH₂COCl, Me₂NCHO, 100°.
- (ii) KOH, H₂O, pyridine, 100°.
- (iii) Na₂S₂O₄, H₂O, Me₂NCHO, heat.

with sodium glyoxal bisulphite to afford the unsubstituted pyrazinoquinoxaline (169). N-Oxygenated derivatives of pyrazinoquinoxalines are unknown and are of particular interest because of their potential synthetic utility as intermediates in the preparation of other pyrazinoquinoxalines.

The synthetic strategy (Scheme 39) adopted for the synthesis of N-oxygenated pyrazinoquinoxalines involved the preparation of ortho-amino-nitroquinoxalinone derivatives (170) and (171) suitable for further elaboration to pyrazinoquinoxalinone N-oxides (172) and (173). The key starting-materials for the proposed synthetic approach ~~were~~ ortho-chloro-nitroquinoxalinones (112) and (113), the preparations of which have been discussed previously. Therefore, the initial investigations (Scheme 40) concentrated on the available 5-chloro-6-nitroquinoxalinones (122b) and (149), amination of which to 5-amino-6-nitroquinoxalinones of the type (174) was successfully accomplished in the previous section (see Schemes 29 and 33). It was anticipated that the amino-nitroquinoxalinones (174) would react with phenylacetyl chloride to give the phenylacetamidoquinoxalinone derivatives (175). Base-catalysed cyclisation of the latter would then give pyrazino-[2,3-f]quinoxalinone N-oxides (176). Cyclisations of this type have been discussed at length in previous chapters.

In practice (Scheme 40) heating the 5-methylamino-6-nitroquinoxalinone (174a) [(174a)=(124d)] with phenylacetyl chloride in dimethylformamide (DMF) at 100° afforded a good yield (91%) of a yellow crystalline solid, which gave analytical and mass spectral data consistent with the formula $C_{23}H_{18}N_4O_4$. The i.r. spectrum of this product contained two carbonyl bands

at 1680 and 1645 cm^{-1} together with absorption due to NH/OH and nitro substituents at 3200-2700, 1525 and 1335 cm^{-1} . The ^1H n.m.r. spectrum of the product contained resonances due to twelve aromatic protons, including the two one-proton doublets at δ 8.27 and 7.64 corresponding to H-7 and H-8 of a 5,6-disubstituted quinoxalinone ring system, as seen for other quinoxalinone derivatives. There were also two singlet resonances at δ 3.40 and 3.30, assigned to a methylene and an N-methyl substituent respectively. The observed analytical and spectroscopic data allowed the formulation of the yellow crystalline solid as 1-methyl-5-(N-methyl,N-phenylacetamido)-6-nitro-3-phenylquinoxalin-2(1H)-one (175a).

Base-catalysed cyclisation of the phenylacetamidoquinoxalinone derivative (175a) using aqueous potassium hydroxide in pyridine afforded an excellent yield of a yellow solid which gave accurate mass data consistent with the pyrazino[2,3-f]-quinoxalinedione N-oxide structure (176a). This structure was further supported by a fragment^{ion} at m/e 380 in the mass spectrum, corresponding to deoxygenation of the product on electron impact. The i.r. and ^1H n.m.r. spectra of the product confirmed the proposed structure (176a). The i.r. spectrum contained bands due to two carbonyl substituents and a broad absorption typical of an NH/OH moiety. The ^1H n.m.r. showed signals due to twelve aromatic protons and a singlet resonance at δ 4.24 corresponding to an N-methyl substituent. Further evidence for the N-oxygenated pyrazinoquinoxalinedione structure (176a) was provided by the reduction of the latter to the pyrazinoquinoxalinedione (177a) on heating with sodium dithionate in aqueous DMF. The analytical and spectroscopic

data of the reduced compound were in accord with the pyrazinoquinoxalinedione structure (177a). The preparation of the pyrazino[2,3-f]quinoxalinedione N-oxide (176a) appears to be the first reported synthesis of an N-oxygenated pyrazinoquinoxaline derivative. A search of the literature provided no previous examples of these compounds. Therefore, efforts were made to extend the synthetic approach to provide further examples of pyrazino[2,3-f]quinoxalinedione N-oxides.

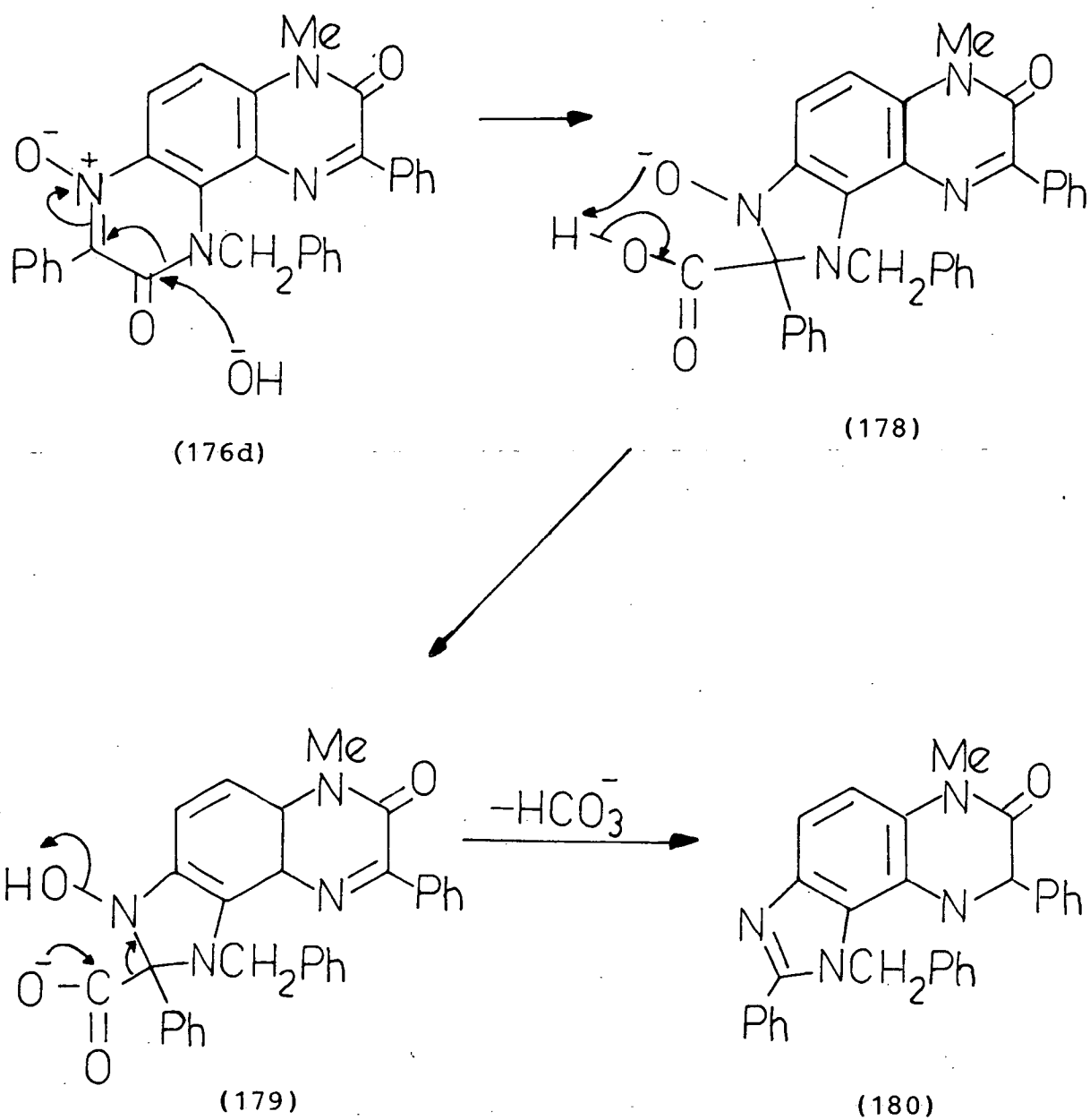
Heating (Scheme 40) the previously prepared 5-chloro-1-N-methyl-6-nitroquinoxalinone [Scheme 33; (149)] with methanolic methylamine in DMF at 50° afforded the methylamino-N-methyl-nitroquinoxalinone (174b) in good yield (92%). The analytical and spectroscopic data of the product were entirely consistent with the methylamino-structure (174b). Heating the latter with phenylacetyl chloride in DMF at 100° afforded a good yield of an orange-yellow solid which gave analytical and spectroscopic data in accord with the phenylacetamidoquinoxalinone structure (175b). The only curious feature being in the i.r. spectrum, which contained only one broad carbonyl absorption at 1660 cm^{-1} . However heating the phenylacetamidoquinoxalinone (175b) with aqueous potassium hydroxide in pyridine gave, after flash-chromatographic work-up, a moderate yield (45%) of a yellow solid which gave analytical and mass spectral data in accord with the pyrazinoquinoxalinedione N-oxide structure (176b). Further evidence for the N-oxygenated structure (176b) was provided by a fragment^{ion} at m/e 394 in the mass spectrum, corresponding to the deoxygenation of the molecular ion at m/e 410. The i.r. spectrum of the product contained two carbonyl bands at 1670 and 1640 cm^{-1} , in accord with the quinoxalinedione

structure (176b). The ^1H n.m.r. provided further evidence for the proposed structure (176b), and in particular contained signals due to two N-methyl substituents at $\delta 4.39$ and 3.83 , together with resonances due to twelve aromatic protons.

Acetylation of the benzylamino-nitroquinoxalinone (174c) [(174c)=(141a)] using phenylacetyl chloride in DMF at 100° afforded a good yield of the phenylacetamidoquinoxalinone (175c) whose combustion analysis and spectroscopic properties were in accord with the assigned structure. The only unusual feature was in the ^1H n.m.r. spectrum, in which the signal due to one of the two methylene groups is as a pair of one-proton doublets. This feature can be explained in terms of the protons of the methylene group being diastereotopic. However the observed coupling constant ($J=14\text{Hz}$) is larger than would be expected for geminal protons held in different magnetic environments. Base-catalysed cyclisation of the product (175c) using aqueous potassium hydroxide in pyridine afforded a moderate yield of a yellow crystalline solid which gave accurate mass data consistent with the molecular formula $\text{C}_{29}\text{H}_{20}\text{N}_4\text{O}_3$. The i.r. spectrum contained carbonyl bands at 1680 and 1640 cm^{-1} together with broad absorption at $3200\text{--}2650\text{ cm}^{-1}$ corresponding to an NH/OH substituent. The ^1H n.m.r. spectrum contained resonances due to seventeen aromatic protons and a singlet at $\delta 6.25$, assigned to the methylene protons of a benzyl substituent. Only one of the expected two one-proton doublets corresponding to H-7 and H-8 of the quinoxalinone ring system was observed, the other being contained in the ten-proton multiplet at $\delta 7.30\text{--}7.20$. The observed accurate mass data and the spectroscopic features of the product

allowed it to be formulated as the benzyl-diphenylpyrazino-[2,3-f]quinoxalinedione N-oxide (176c). A fragment^{ion} at m/e 456 in the mass spectrum, corresponding to deoxygenation of the product, gave further evidence for the assigned structure (176c). Reduction of the N-oxide (176c) to the corresponding pyrazinoquinoxalinedione (177c) using sodium dithionate in aqueous DMF went in high yield. The reduced product (177c) gave combustion analysis and spectroscopic data in accord with the assigned structure.

Heating (Scheme 40) the benzylamino-1-N-methyl-nitroquinoxalinone (174d) [(174d)=(153)] with phenylacetyl chloride in DMF afforded a good yield of the expected phenylacetamidoquinoxalinone (175d), which gave analytical data consistent with the assigned structure. However, the mass spectrum contained a parent ion at ($M^+ + 1$) 505 and not the expected molecular ion at m/e 504. The ^1H n.m.r. spectrum of the compound again showed two one-proton doublets corresponding to diastereotopic protons of a methylene substituent. Curiously the benzyl CH_2 protons gave two one-proton singlet resonances at δ 3.44 and 3.40, presumably because they are held in different magnetic environments. The base-catalysed cyclisation of the phenylacetamidoquinoxalinone (175d) did not give the expected pyrazino[2,3-f]quinoxalinedione N-oxide (176d). Heating the phenylacetamido derivative (175d) with aqueous potassium hydroxide in pyridine afforded a yellow solid which gave analytical and mass spectral data consistent with the molecular formula $\text{C}_{30}\text{H}_{22}\text{N}_4\text{O}_3$. The i.r. spectrum of the product contained only a carbonyl band at 1650 cm^{-1} . The ^1H n.m.r. spectrum showed proton resonances due to seventeen

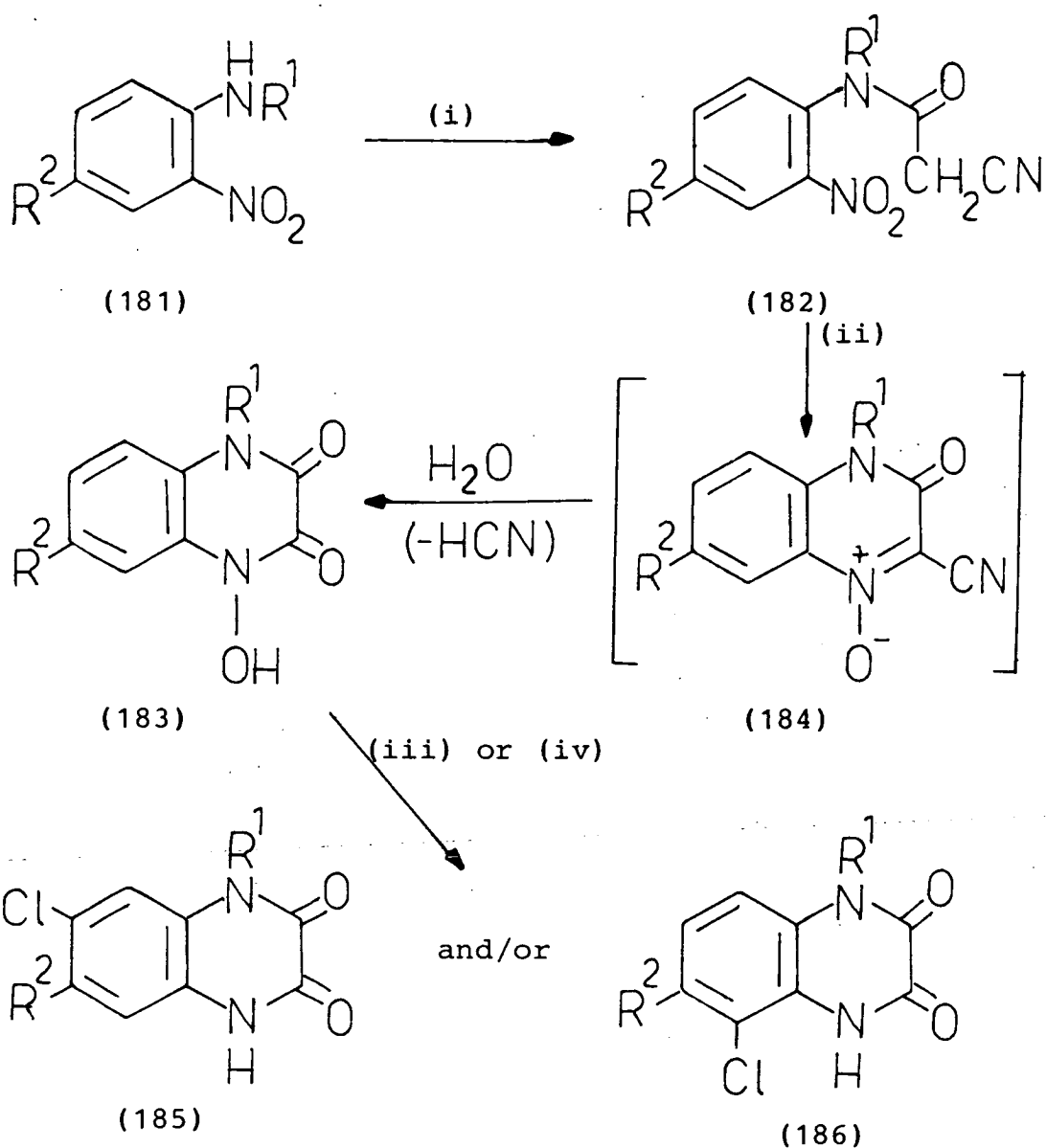


Scheme 41

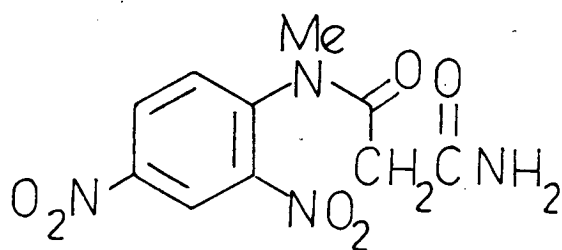
aromatic protons at δ 8.13-6.96, together with two singlets at δ 6.08 and 3.80 characteristic of a methylene and an N-methyl substituent respectively. The observed analytical and spectroscopic properties were consistent with the imidazoquinoxalinone structure [Scheme 41; (180)]. The mechanism for the formation of the product is outlined in Scheme 41. The initial product formed on treatment of the phenylacetamidoquinoxalinone (175d) with base was the quinoxalinedione N-oxide (176d) which then further reacts under the basic conditions to give an imidazoquinoxalinone intermediate (178). Proton transfer followed by elimination of a bicarbonate anion gives the observed product (180). Analogous ring contractions of quinoxaline N-oxides to benzimidazole derivatives have been reported in the literature.¹⁷⁵

Having been successful in preparing (Scheme 39) N-oxygenated pyrazinoquinoxalinedione derivatives of the type (173) (see Scheme 40) from 5-chloro-6-nitroquinoxalinone precursors (113) attention was turned to the synthesis of 7-chloro-6-nitroquinoxalinone precursors (112) suitable for further elaboration to pyrazinoquinoxalinedione N-oxides (172). The proposed synthesis of the 7-chloro-6-nitroquinoxalinones (112) involved chlorination of an N-oxygenated quinoxalinone and reactions of this type have been discussed above. It is postulated that the chlorination can be influenced by substituents on the quinoxalinone ring system to give the desired product (112). Therefore, attempts were made to prepare a range of N-oxygenated quinoxalinone derivatives with a view to investigating their chlorination.

The synthesis (Scheme 42) of α -cyano-2-nitroacetanilide



	<u>R¹</u>	<u>R²</u>
a;	H	H
b;	H	NO ₂
c;	Me	NO ₂



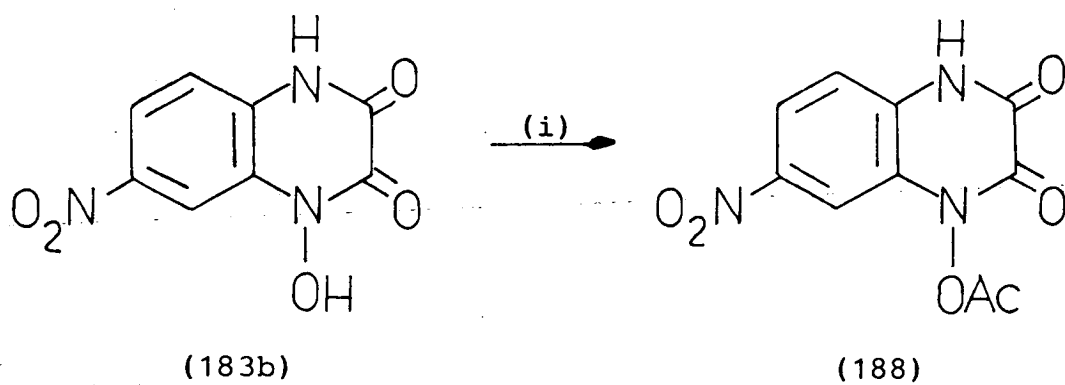
- (i) $CNCH_2COCl$, C_6H_6 , heat.
- (ii) KOH , H_2O , heat or $NaOEt$, $EtOH$, heat or KOH , H_2O , pyridine,
- (iii) $AcCl$, $AcOH$, heat.
- (iv) $Me C_6H_4SO_2Cl$, Me_2NCHO , heat.

(182a) and its subsequent base-catalysed cyclisation to an N-hydroxyquinoxalinedione (183a) has been reported in the literature.⁷⁴ Reaction of the product (183a) with acetyl chloride in glacial acetic acid is known¹⁵⁹ to give the 6-chloroquinoxalinedione (185a). It was of interest in the present studies to prepare the nitroquinoxalinedione derivatives (183b) and (183c) with a view to studying their chlorination. Heating 2,4-dinitroaniline with cyanoacetyl chloride⁷⁴ in dry benzene afforded a quantitative yield of the α -cyanoacetanilide (182b). The combustion analysis and mass spectral data were in accord with the assigned structure (182b). Its i.r. spectrum contained an amide carbonyl band at 1710 and absorptions at 3300, 2200 and 1500 and 1350 cm^{-1} due to an NH, a cyano and a nitro substituent. The ^1H n.m.r. spectrum contained as expected, two one-proton doublets and a one-proton doublet at δ 8.73, 7.99 and 8.55 corresponding to H-3, H-6 and H-5 of the α -cyanoacetanilide (182b). Singlet resonances at δ 11.01 and 4.11 were assigned to the NH and the methylene substituents of the acetamide side-chain.

Similarly, heating 2,4-dinitro-N-methylaniline (181c) with cyanoacetyl chloride in dry benzene afforded a moderate yield of the α -cyanoacetanilide (182c) on flash-chromatographic work-up of the reaction mixture. The analytical and spectroscopic properties of the product are entirely consistent with the assigned structure (182c). Unreacted starting-material (181c) and a cream crystalline solid which gave analytical data consistent with the molecular formula $\text{C}_{10}\text{H}_{10}\text{N}_4\text{O}_6$ were also isolated from the reaction mixture. The mass spectrum of the cream solid contained a molecular ion at $(\text{M}^+ + 1)$, 283 and not

at m/e 282 as expected. The i.r. spectrum contained two amide carbonyl bands at 1690 and 1660 cm^{-1} , together with NH and nitro absorptions at 3370, 3170, 1490 and 1355 cm^{-1} . The ^1H n.m.r. of the product at 85° contained two one-proton doublet resonances and a one-proton double doublet resonance characteristic of a 1,2,4-trisubstituted benzene ring, together with singlets at δ 6.97, 3.25, 3.12 and 3.06. The signals at δ 6.97 and 3.25 were assigned to the protons of an NH_2 and an NCH_3 group respectively, while the remaining one-proton singlet resonances at δ 3.12 and 3.06 were assigned to magnetically non-equivalent protons of a methylene substituent. The observed analytical and spectroscopic properties of the product are consistent with the N-methoxymalonamide derivative (187) which presumably results from hydrolysis of the α -cyanoacetamide (182c) on work-up of the reaction mixture.

The attempted base-catalysed cyclisation of the α -cyanoacetanilide (182b) using sodium ethoxide and aqueous sodium hydroxide in pyridine failed to give the expected quinoxalinedione derivative (183b). The only products isolated from these reactions being dark intractable solids or unreacted starting-material (182b). However, heating the α -cyanoacetanilide in aqueous potassium hydroxide afforded a brown crystalline solid which gave accurate mass data consistent with the molecular formula $\text{C}_8\text{H}_5\text{N}_3\text{O}_5$. The i.r. spectrum of the product contained carbonyl and nitro absorption at 1690, 1540 and 1335 cm^{-1} , together with a broad band at 3600-3200 cm^{-1} attributed to NH and OH substituents. The ^1H n.m.r. spectrum contained two one-proton doublets and a one-proton double doublet at δ 8.02, 8.00 and 7.34, together with a broad



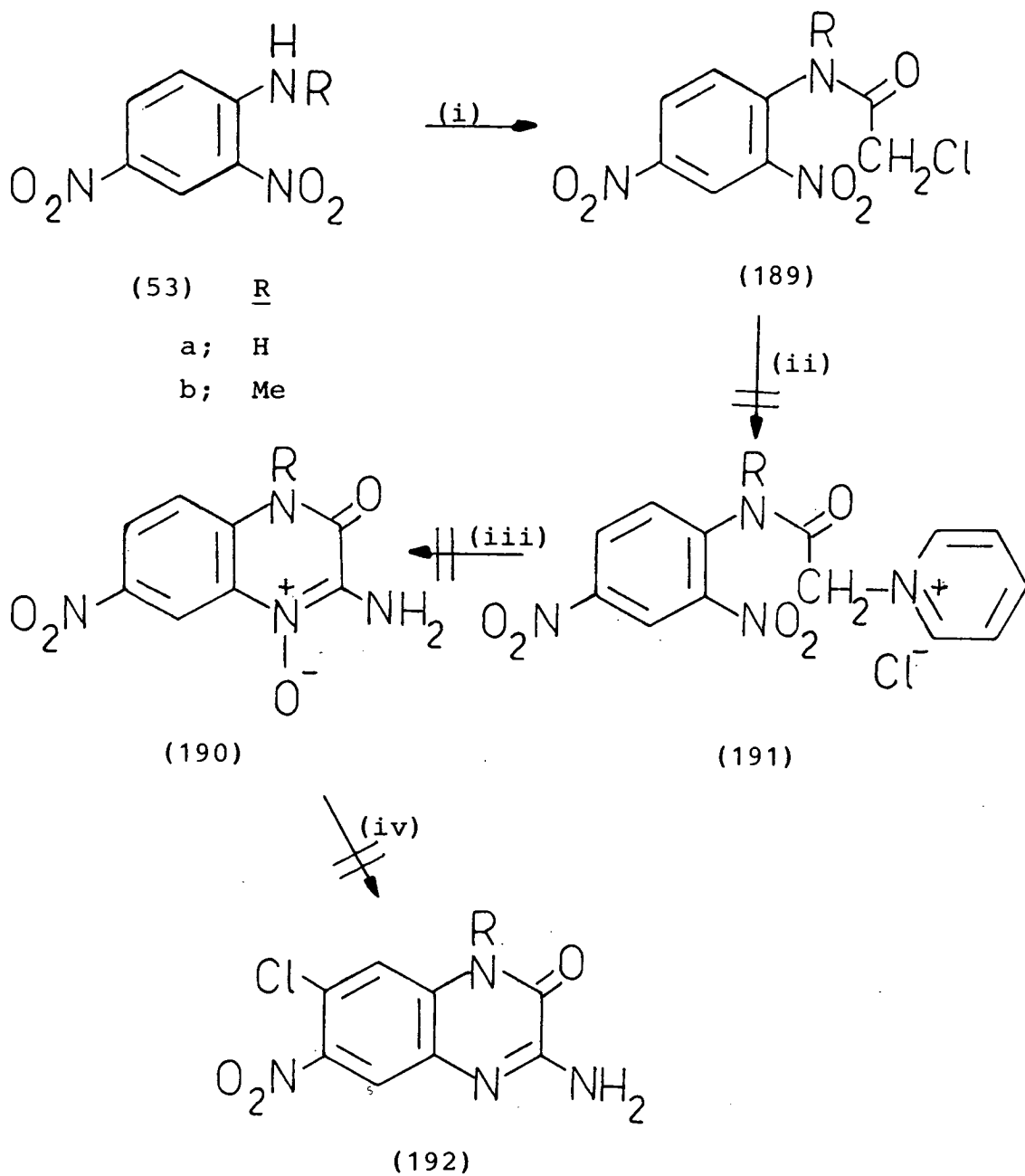
(i) AcCl, AcOH, heat.

Scheme 43

singlet at $\delta 12.03$ due to NH and OH substituents. The observed accurate mass and spectroscopic properties are in accord with the N-hydroxyquinoxalinedione structure (183b). The proposed mechanism⁷⁴ for the formation of the quinoxalinedione product (183b) involves base-catalysed cyclisation of the α -cyanoacetanilide (182b) to an intermediate cyanoquinoxalinone N-oxide (184b) hydrolysis of which accounts for the formation of the observed product (183b).

Treatment of the α -cyano-N-methylacetanilide (182c) with either aqueous potassium hydroxide under reflux or aqueous sodium hydroxide in pyridine at room temperature, failed to give the N-hydroxy-N-methylquinoxalinedione derivative (183c). The only products isolated from both these reactions were a series of intractable solids. However heating a suspension of the α -cyanoacetanilide (182c) with sodium ethoxide in ethanol afforded the quinoxalinedione (183c) in moderate yield (57%). The combustion analysis of the product was in accord with a monohydrate of the N-hydroxy-N-methylquinoxalinedione structure (183c) and its mass, i.r. and ^1H n.m.r. spectra confirmed the assigned structure.

The attempted chlorination of the N-hydroxyquinoxalinedione (183b) using the usual acetyl chloride-glacial acetic acid conditions failed to give either of the ortho-chloro-nitroquinoxalinedione derivatives (185b) or (186b). The only product isolated on heating the quinoxalinedione (183b) with acetyl chloride in glacial acetic acid was a solid, tentatively formulated as the acetoxo derivative [Scheme 43; (188)]. The i.r. spectrum of the product contained a carbonyl band at 1810 cm^{-1} characteristic of an acetoxo substituent, together with



(i) ClCH_2COCl , C_6H_6 , heat.

(ii) pyridine, heat.

(iii) base.

(iv) AcCl , AcOH , heat.

absorption due to NH/OH , amide carbonyl and nitro substituents at 3680-2600, 1720 and 1535 and 1340 cm^{-1} . The attempted purification of the acetoxyquinoxalinedione (188) by crystallisation for combustion analysis, gave the N-hydroxyquinoxalinedione (183b), as did hydrolysis using aqueous sodium hydroxide. However (Scheme 42) heating the N-hydroxyquinoxalinedione (183b) with toluene-*p*-sulphonyl chloride (tosyl chloride) in dimethylformamide afforded a moderate yield (45%) of a cream crystalline solid which gave accurate mass data consistent with the molecular formula $\text{C}_8\text{H}_4\text{ClN}_3\text{O}_4$. The i.r. spectrum of the product contained two amide carbonyl bands at 1700 and 1650 cm^{-1} together with NH and nitro absorptions at 3580-3250 and 1535 and 1340 cm^{-1} . The ^1H n.m.r. of the product contained two one-proton doublets at δ 7.83 and 7.19, together with a band signal at δ 12.14 assigned to the protons of two NH substituents. The observed accurate mass and spectroscopic properties of the product are consistent with the 5-chloro-6-nitroquinoxalinedione structure (186b). Due to the isolation of this product as opposed to the hoped for 7-chloro derivative (185b), and because time was running short, no further attempts were made to investigate the chemistry of the N-hydroxyquinoxalinediones (183).

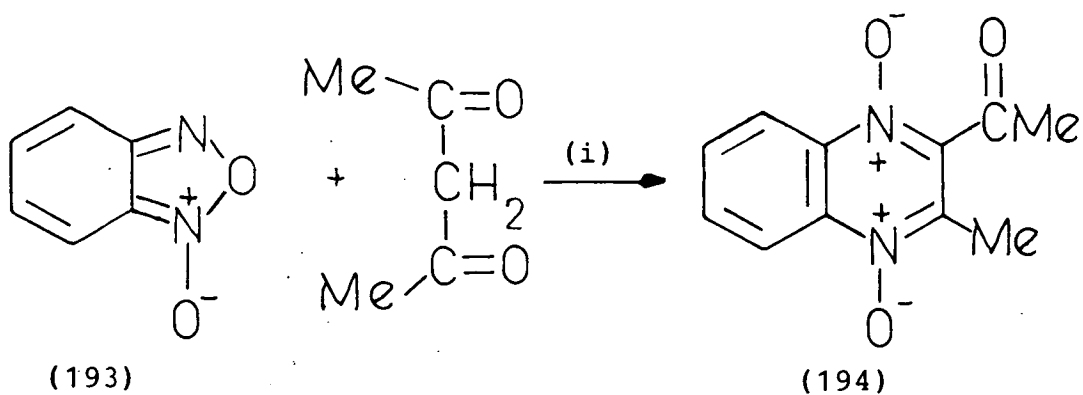
Efforts were made (Scheme 44) to obtain the quinoxalinone N-oxides (190), chlorination of which might provide the 7-chloro-6-nitro derivatives (192). The possible directing effect on the site of chlorination by substituents in quinoxalinone N-oxides has been discussed above. The synthesis of α -chloro-2-nitroacetanilides and the corresponding pyridinium salts has been reported in the literature.⁸⁰ The latter are

known⁸⁰ to cyclise under base-catalysed conditions with degradation of the pyridine ring to give aminoquinoxalinone N-oxides. In these studies the synthesis (Scheme 44) of 2,4-dinitroacetamido-pyridinium salts (191) were investigated, with a view to obtaining the required quinoxalinone N-oxides (190) on base-catalysed cyclisation.

Heating 2,4-dinitroaniline (53a) with commercially available chloroacetyl chloride in dry benzene afforded, on flash-chromatographic work-up of the reaction mixture, a good yield of the α -chloroacetanilide (189a). The combustion analysis and spectroscopic data of the product were consistent with the assigned structure (189a). However the reaction of 2,4-dinitro-N-methylaniline (53b) with chloroacetyl chloride in dry benzene did not give the corresponding α -chloroacetanilide (189b). The only products isolated from this reaction were unreacted starting-material (53b) and an unresolved solid mixture. The reaction of the α -chloroacetanilide (189a) with pyridine failed to give the expected pyridinium salt (191a), the only product isolated being a dark intractable glass which was not further investigated.

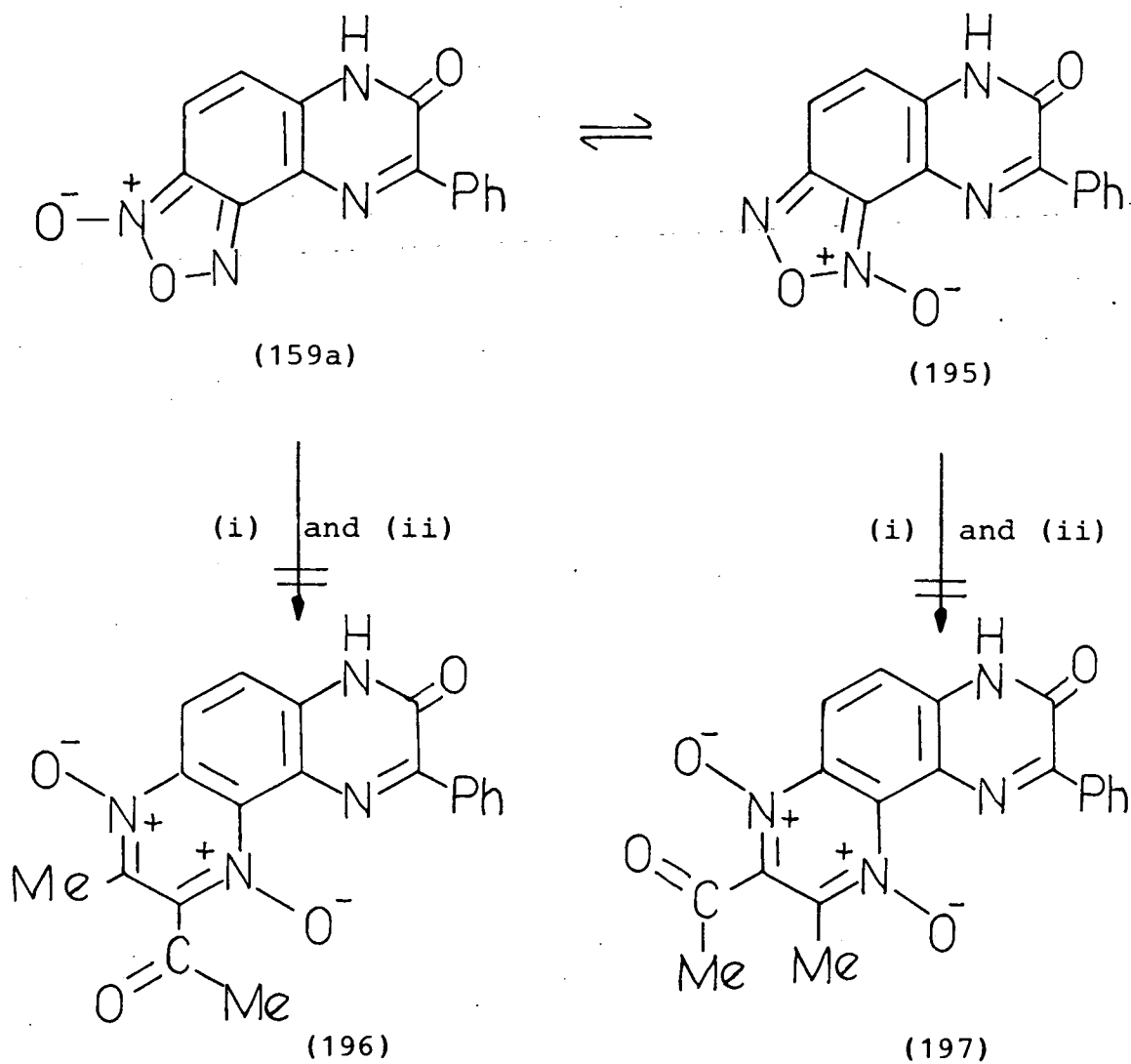
The failure (Scheme 44) to effect the synthesis of a pyridinium salt of type (191) prevented the proposed investigation into their base-catalysed cyclisation to quinoxalinone N-oxide derivatives (190). Thus, also preventing the preparation of the chloro-nitroquinoxalinone derivatives (192) required for elaboration to N-oxygenated pyrazinoquinoxalinones.

The reaction of benzofuroxan derivatives with β -diketones in the presence of triethylamine is known¹⁷⁶ to give 2-acyl-quinoxaline N,N-dioxides. Reactions of this type are



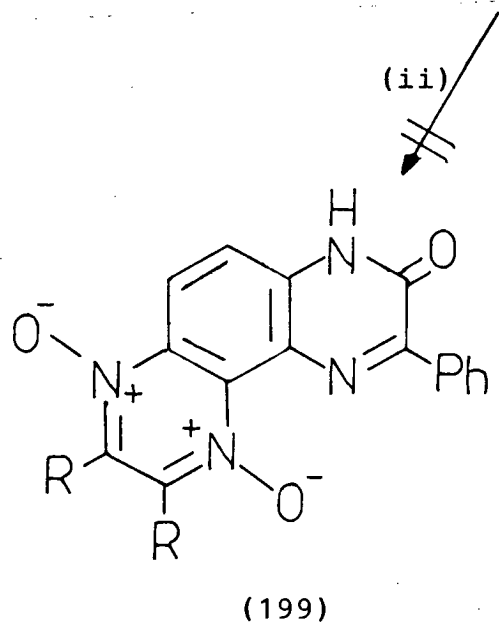
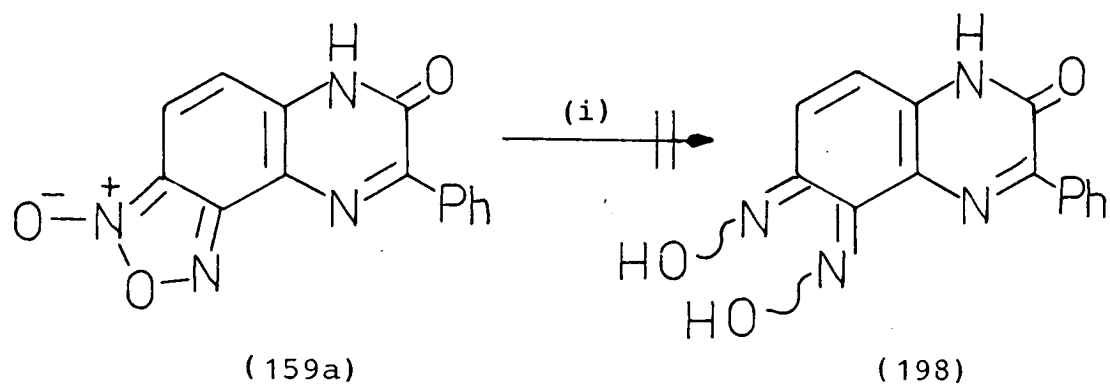
(i) Et₃N.

Scheme 45



(i) MeC(=O)CH₂C(=O)Me, Et₃N, Me₂NCHO.
(ii) MeC(=O)CH₂C(=O)Me, piperidine, Me₂NCHO.

Scheme 46



(i) NaBH_4 , $(\text{CH}_3\text{OCH}_2\text{CH}_2)_2\text{O}$.

(ii) $\text{RC}(=\text{O})\text{CHOHR}$.

Scheme 47

exemplified (Scheme 45)¹⁷⁷ by reaction of benzofuroxan (193) with acetylacetone to give the quinoxaline N,N-dioxide (194). Further, it was shown¹⁷⁸ that reactions of this type involve an initial attack by carbanions produced in situ on the intact furoxan ring. The reaction (Scheme 46) of the oxadiazoloquinoxalinone N-oxide (159a) with β -diketones was investigated, with a view to obtaining novel pyrazinoquinoxalinone N,N-dioxides e.g. (196) and (197). The oxadiazoloquinoxalinone N-oxide (159a) can exist in the tautomeric form (195), but this tautomer was considered to be less favourable than (159a) due to steric hindrance. Therefore, the expected product from reaction of the oxadiazoloquinoxalinone N-oxide (159a) with acetylacetone was the pyrazinoquinoxalinone N,N-dioxide (196).

In practice treatment of the oxadiazoloquinoxalinone N-oxide (159a) with acetylacetone in DMF in the presence of triethylamine afforded only unreacted starting-material (159a). Similarly treatment with acetylacetone in DMF in the presence of piperidine also gave unreacted oxadiazoloquinoxalinone N-oxide (159a) and not the expected N,N-dioxide (196). The failure of this reaction can be explained in terms of steric hindrance around the oxadiazoloquinoxalinone N-oxide ring system. Therefore an alternative approach to a pyrazinoquinoxalinone N,N-dioxide was investigated.

Dialkylfuroxans, diarylfuroxans and benzofuroxans can be¹⁷⁶ reduced by sodium borohydride to dioximes and it was interesting in the present studies (Scheme 47), to attempt the reduction of the oxadiazoloquinoxalinone N-oxide (159a). The expected product from this reduction was the dioxime (198) which could potentially react with α -hydroxyketones to

give a pyrazoloquinoxalinone N,N-dioxide (199). In practice the attempted reduction of the oxadiazoloquinoxalinone N-oxide (159a) using sodium borohydride in diethylene glycol dimethyl ether, failed to give the dioxime (198). The only product isolated from this reaction was unreacted starting-material (159a). Thus, the proposed investigation into the formation of a pyrazoloquinoxalinone N,N-dioxide (199) by reaction of the dioxime (198) with α -hydroxyketones could not be carried out. Due to lack of time no further attempts were made to obtain the dioxime (198) using alternative reducing agents, and the synthetic approach to pyrazoloquinoxalinone N,N-dioxides (199) was abandoned at this stage.

(v) ExperimentalThe Reaction of 2,4-Dinitroaniline with Formaldehyde and Sodium Cyanide in the Presence of Zinc Chloride

A suspension of 2,4-dinitroaniline (1.8 g, 0.01 mol), paraformaldehyde (0.91 g, 0.03 mol), sodium cyanide (1.5 g, 0.03 mol) and powdered anhydrous zinc chloride (10.2 g, 0.075 mol) in glacial acetic acid (25.0 ml) was stirred at 50° (oil bath) for 6h. The resulting suspension was treated with water (35.0 ml) and the solid obtained collected, heated under reflux with water (15.0 ml) for a few min, then refiltered to afford an uncharacterised solid (1.7 g; 86%) which formed yellow needles m.p. 279-280° (from ethanol-dimethylformamide), ν_{\max} 3340 (NH) and 1500 and 1350 (NO₂) cm⁻¹.

Found: C, 41.7; H, 2.6; N, 21.4%; M⁺, 195.0289.
C₇H₅N₃O₄ requires: C, 43.1; H, 2.6; N, 21.5%; M, 195.0280.

Heating a solution of the uncharacterised solid (0.39 g, 0.002 mol) and 20% w/v aqueous sulphuric acid (5.0 ml) in glacial acetic acid (20.0 ml) under reflux for 17h, followed by concentration of the mixture to one third of the original volume and dilution with water (5.0 ml) gave 2,4-dinitroaniline (0.36 g; 98%) m.p. 180-185° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

2,4-Dinitro-N-methylaniline (53b)

2,4-Dinitro-N-methylaniline (53b) was prepared (yield 41%) by the reaction of 2,4-dinitrochlorobenzene with ethanolic methylamine as described by Le Bris,¹⁵⁶ and had m.p. 175-179° (lit.,¹⁵⁶ 178°).

The Attempted Reaction of 2,4-Dinitro-N-methylaniline (53b) with Formaldehyde and Sodium Cyanide in the Presence of Zinc Chloride

A solution of 2,4-dinitro-N-methylaniline (53b) (1.9 g, 0.01 mol) in glacial acetic acid (25.0 ml) and dimethylformamide (30.0 ml) was stirred and treated at 50° (oil bath) with paraformaldehyde (0.9 g, 0.03 mol), powdered zinc chloride (10.2 g, 0.075 mol) and sodium cyanide (1.5 g, 0.03 mol) and the mixture was stirred at 50° for 6h. The resulting solution was treated with hot water (50.0 ml) and filtered to give a solid which was combined with a second crop obtained by extraction of the aqueous mother liquor with methylene chloride, evaporation of the extract and trituration of the resulting residue with ethanol to give unreacted 2,4-dinitro-N-methylaniline (53b) (1.4 g; 75%) identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the ethanolic liquor afforded a brown oil (1.2 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture which was not further investigated.

Diphenylphosphinamide (68)

Diphenylphosphinamide (68) was prepared (yield 59%) by the reaction of diphenylphosphinyl chloride (69) with aqueous ammonia at 0-10° (ice-bath) as described by Zwierzak,¹⁵⁸ and had m.p. 159-162° (lit.,¹⁵⁸ 165-167°).

N-(2,4-Dinitrophenyl)diphenylphosphinamide (70)

(a) A stirred suspension of diphenylphosphinamide (68) (1.1 g, 0.005 mol), powdered sodium hydroxide (0.92 g, 0.002 ml) and potassium carbonate (0.07 g, 0.0005 mol) in benzene (50.0 ml)

was heated under reflux and treated dropwise over 0.5h with a solution of 2,4-dinitrochlorobenzene (1.2 g, 0.006 mol) in benzene (25.0 ml), and the mixture was stirred at reflux for a further 2.5h. The resulting dark solution was treated with water (50.0 ml) and extracted with benzene (2x50.0 ml). The combined extracts were washed with portions of water (25.0 ml) until the aqueous phase was neutral then the organic phase was evaporated and the residue triturated with ether to give N-(2,4-dinitrophenyl)diphenylphosphinamide (70) (0.77 g; 40%) which formed cream crystals m.p. 155-156° (from toluene), ν_{\max} 3280 (NH) and 1530, 1510, 1345 and 1330 (NO₂) cm⁻¹, δ (CDCl₃) 9.44 (1H, br s, NH), 9.10 (1H, d, J8.5Hz, ArH), 8.27-7.38 (11H, m, ArH) and 7.25 (1H, s, ArH).

Found: C, 56.5; H, 3.4; N, 10.5%; M⁺, 383.

C₁₈H₁₄N₃O₅P requires: C, 56.4; H, 3.7; N, 11.0%; M, 383.

The ethereal filtrate was evaporated to give a brown gum (0.29 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture, which was not further investigated.

The aqueous mother liquor was acidified with concentrated hydrochloric acid to give impure unreacted diphenylphosphinamide (68) (0.56 g; 51%) m.p. 145-150°, identical (i.r. spectrum) to an authentic sample.

(b) A vigorously stirred suspension of sodium hydride (1.1 g, 0.044 mol) in dry dimethylformamide (20.0 ml) was treated with a solution of 2,4-dinitroaniline (3.7 g, 0.02 mol) in dry dimethylformamide (25.0 ml) and the mixture stirred at room temperature for 15 min. A solution of diphenylphosphinyl chloride (6.0 g, 0.02 mol) in dry dimethylformamide

(20.0 ml) was then added dropwise and the mixture stirred at room temperature for 19h. The resulting solution was treated with water (100 ml) and extracted with methylene chloride to give a yellow solid which was crystallised from toluene to afford N-(2,4-dinitrophenyl)diphenylphosphinamide (70) (5.7 g; 75%) m.p. 148-152°, identical (m.p. and i.r. spectrum) to an authentic sample prepared in (a) before.

The toluene filtrate was evaporated to give a brown gum (2.1 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture, which was not further investigated.

(c) A solution of 2,4-dinitroaniline (0.37 g, 0.002 mol) in dry benzene (50.0 ml) was treated with a solution of diphenylphosphinyl chloride (0.61 g, 0.002 mol) in dry benzene (50.0 ml) and the mixture was heated under reflux for 1h. The resulting solution was evaporated and the residue triturated with ether to give impure unreacted 2,4-dinitroaniline (0.23 g; 62%) m.p. 160-165°, identical (i.r. spectrum) to an authentic sample.

The ethereal filtrate was evaporated to give a solid (0.43 g) whose i.r. spectrum suggested it was 2,4-dinitroaniline contaminated with diphenylphosphinyl chloride.

The Attempted Reaction of N-(2,4-Dinitrophenyl)diphenylphosphinamide (70) with Chloroacetonitrile

(a) A two-phase mixture of N-(2,4-dinitrophenyl)diphenylphosphinamide (70) (0.38 g, 0.001 mol), chloroacetonitrile (0.15 g, 0.002 mol) and tetrabutylammonium hydrogen sulphate (0.02 g, 0.00005 mol) in benzene (5.0 ml) and 50% w/v aqueous

sodium hydroxide (5.0 ml) was stirred and heated under reflux for 3h. The suspension was treated with water (10.0 ml) and benzene (100 ml), the resulting three-phase system filtered, the solid slurried with aqueous 2M hydrochloric acid and collected to give impure unreacted phosphinamide (70) (0.16 g; 42%) m.p. 130-135° (decomp.) identical (i.r. spectrum) to an authentic sample.

Evaporation of the organic phase gave a brown gum (0.12 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture containing the unreacted phosphinamide (70) and 2,4-dinitroaniline.

(b) A vigorously stirred suspension of sodium hydride (0.05 g, 0.0022 mol) in dry dimethylformamide (2.0 ml) was treated with a solution of N-(2,4-dinitrophenyl)diphenylphosphinamide (70) (0.77 g, 0.002 mol) in dry dimethylformamide (5.0 ml) and the mixture was stirred at room temperature for 0.5h, then treated dropwise with a solution of chloroacetonitrile (0.17 g, 0.0022 mol) in dry dimethylformamide (2.0 ml) and stirring continued at room temperature for 17h. The resulting solution was treated with water (20.0 ml) and extracted with methylene chloride to give the unreacted phosphinamide (70) (0.76 g; 99%) m.p. 140-144°, identical (m.p. and i.r. spectrum) to an authentic sample.

6-Nitrobenzofuroxan (72)

6-Nitrobenzofuroxan (72) was prepared (yield 40%) by the diazotisation of 2,4-dinitroaniline with sodium nitrite followed by reaction with sodium azide at 0° (ice-salt bath) as described by Mallory and Varimby,¹⁶⁰ and had m.p. 64-68°

(lit.,¹⁶⁰ 68-70°).

The Attempted Reaction of 6-Nitrobenzofuroxan (72) with Formaldehyde in Methanolic Potassium Hydroxide

A vigorously stirred suspension of 6-nitrobenzofuroxan (72) (1.8 g, 0.01 mol) in methanol (5.0 ml) and water (5.0 ml) was treated at room temperature with 40% w/v aqueous formaldehyde solution (0.75 g), a solution of potassium hydroxide (1.2 g, 0.02 mol) in water (1.0 ml) and methanol (1.0 ml) was added dropwise and the resulting mixture heated at 40-50° (water bath) for 1h. The reaction mixture was then diluted with water (10.0 ml) and acidified with concentrated hydrochloric acid to give a dark brown intractable solid (1.1 g) from which no identifiable material was obtained.

The aqueous acidic mother liquor was extracted with methylene chloride to give a brown gum (0.26 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture, which was not further investigated.

2,4-Dinitrobenzoyl Chloride (92)

A mixture of 2,4-dinitrobenzoic acid (10.6 g, 0.05 mol) and phosphorous pentachloride (14.6 g, 0.07 mol) was stirred with exclusion of atmospheric moisture at 100° (oil bath) for 4h. The oily mixture was extracted with boiling dry light petroleum then with boiling dry toluene and the combined extracts evaporated to give 2,4-dinitrobenzoyl chloride (92) as a yellow oil (11.4 g; 99%) (lit.,¹⁶² m.p. 42-46°), ν_{\max} 1790 br (CO) and 1540 br, and 1350 br, (NO₂) cm⁻¹, δ (CDCl₃) 8.93 (1H, d, J₂Hz, H-3), 8.67 (1H, dd, J_{ortho} 8.5Hz, J_{meta} 2Hz,

H-5) and 7.92 (1H, d, J8.5Hz, H-6).

N-Cyanomethyl-N-methyl-2,4-dinitrobenzamide (93)

A suspension of N-methylaminoacetonitrile hydrochloride (2.1 g, 0.02 mol) and fused sodium acetate (7.6 g) in glacial acetic acid (50.0 ml) was stirred and treated dropwise at room temperature with 2,4-dinitrobenzoyl chloride (92) (4.6 g, 0.02 mol) and the mixture was stirred at room temperature for 3h. The resulting suspension was evaporated, the residue treated with water (25.0 ml) and the solid collected to afford N-cyanomethyl-N-methyl-2,4-dinitrobenzamide (93) (4.7 g; 89%), which formed colourless crystals m.p. 153-154° (from ethanol-dimethylformamide), ν_{\max} 1660 (CO) and 1525 and 1350 (NO₂) cm⁻¹, $\delta[(\text{CD}_3)_2\text{SO}]$ 8.92-8.61 (2H, m, ArH), 7.97-7.84 (1H, m, ArH), 4.66 (2H, s, CH₂), 4.46 (2H, s, CH₂), 3.13 (3H, s, NCH₃) and 2.90 (3H, s, NCH₃) changing at 87° to $\delta[(\text{CD}_3)_2\text{SO}]$ 8.91 (1H, d, J2.2Hz, H-3), 8.67 (1H, dd, J_{ortho} 8.4Hz, J_{meta} 2.2Hz, H-5), 7.90 (1H, d, J8.4Hz, H-6), 4.65 (2H, s, CH₂) and 3.10 (3H, s, NCH₃).

Found: C, 45.2; H, 3.1; N, 21.5%; M⁺, 264.

C₁₀H₈N₄O₅ requires: C, 45.5; H, 3.1; N, 21.2%; M, 264.

7-(2,3-Dioxo-1-hydroxy-3-methyl-1,2,3,4-tetrahydroquinazolin-7-yl)azo-2,3-dioxo-1-hydroxy-3-methyl-1,2,3,4-tetrahydroquinazoline (95)

A suspension of N-cyanomethyl-N-methyl-2,4-dinitrobenzamide (93) (0.26 g, 0.001 mol) in absolute ethanol (12.5 ml) was treated with a solution of sodium (0.09 g, 0.004 g.atom) in absolute ethanol (2.5 ml) and the mixture was heated under

reflux for 1h. The mixture was evaporated and the residue treated with water (5.0 ml) and acidified with concentrated hydrochloric acid to give 7-(2,3-dioxo-1-hydroxy-3-methyl-1,2,3,4-tetrahydroquinazolin-7-yl)azo-2,3-dioxo-1-hydroxy-3-methyl-1,2,3,4-tetrahydroquinazoline (95) (0.18 g; 84%), which formed yellow crystals m.p. $>330^{\circ}$ (from dimethylformamide-water), ν_{\max} 3400 br, w, (OH) and 1710 and 1665 (CO) cm^{-1} .

Found: C, 50.2; H, 4.3; N, 19.2%; M^+ , 410.0716.

$C_{18}N_{14}O_6$ requires: C, 50.5; H, 3.7; N, 19.6%; M , 410.0975.

The aqueous mother liquor was extracted with methylene chloride to give a red-brown gum (<0.01 g) which was not further investigated.

The Attempted Reaction of 7-(2,3-Dioxo-1-hydroxy-3-methyl-1,2,3,4-tetrahydroquinazolin-7-yl)azo-2,3-dioxo-1-hydroxy-3-methyl-1,2,3,4-tetrahydroquinazoline (95) with Acetic Anhydride

A suspension of the azoquinazoline derivative (95) (0.24 g, 0.0005 mol) in acetic anhydride (2.0 ml) was heated at 100° (water bath) for 10 min. The solution was treated with ether and the precipitated solid was collected to give an intractable brown solid (0.20 g) whose t.l.c. in ethanol over silica showed it to be a close running mixture, which was not further investigated.

4-Chloro-2-nitrobenzoyl Chloride (100)

4-Chloro-2-nitrobenzoyl chloride (100) was prepared (yield quantitative) by the reaction of 4-chloro-2-nitrobenzoic acid with thionyl chloride as described by Cohen and Armes,¹⁶⁴ and had m.p. $33-35^{\circ}$ (lit.,¹⁶⁴ $34-36^{\circ}$).

N-Cyanomethyl-N-methyl-4-chloro-2-nitrobenzamide (101)

N-Cyanomethyl-N-methyl-4-chloro-2-nitrobenzamide (101) was prepared (yield 91%) by the reaction of 4-chloro-2-nitrobenzoyl chloride (100) with N-methylaminoacetonitrile hydrochloride as described by Bayne and Tennant,¹⁶³ and had m.p. 127-130° (lit.,¹⁶³ 128-129°).

7-Chloro-1-hydroxy-3-methylquinazoline-2,4(1H,3H)-dione (103)

7-Chloro-1-hydroxy-3-methylquinazoline-2,4(1H,3H)-dione (103) was prepared (yield 91%) by the ethanolic sodium ethoxide catalysed cyclisation of N-cyanomethyl-N-methyl-4-chloro-2-nitrobenzamide (101) as described by Bayne and Tennant,¹⁶³ and had m.p. 255-258° (lit.,¹⁶³ 263-265°).

The Nitration of 7-Chloro-1-hydroxy-3-methylquinazoline-2,4(1H,3H)-dione (103)

(a) A solution of 7-chloro-1-hydroxy-3-methylquinazolin-2,4(1H,3H)-dione (103) (1.1 g, 0.005 mol) in concentrated sulphuric acid (5.0 ml) was treated dropwise with stirring at 0° (ice-salt bath) with fuming nitric acid (S.G. 1.52) (0.2 ml) and the mixture was stirred at 0° for 15 min then heated at 100° (water bath) for 20 min. The reaction mixture was then poured onto crushed ice (25.0 g) to give a solid which was stirred as a suspension in saturated aqueous sodium hydrogen carbonate solution (15.0 ml) for 0.5h. Acidification of the suspension with concentrated hydrochloric acid afforded an orange solid which was collected and well washed with water and ethanol to give a solid, tentatively formulated as 7-chloro-1-hydroxy-3-methyl-6-nitroquinazoline-2,4(1H,3H)-dione (102)

(0.60 g; 44%), which formed brown crystals m.p. 325-327° (from dimethylformamide-water), ν_{\max} 3700-3200 br (OH), 1735 (CO) and 1540 and 1340 (NO_2) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 12.01 (1H, s, OH), 8.51 (1H, s, H-5), 7.33 (1H, s, H-8) and 3.32 (3H, s, NCH_3).

Found: M^+ , 273 and 271.

$\text{C}_9\text{H}_6\text{ClN}_3\text{O}_5$ requires: M , 273 and 271.

The aqueous acidic filtrate was extracted with methylene chloride to give a gum (<0.01 g) which was not further investigated.

The ice cold aqueous mother liquor was extracted with ethyl acetate to give an orange-brown gum (0.74 g) whose t.l.c. in ethanol over silica showed it to be a complex mixture, which was not further investigated.

(b) A mixture of concentrated sulphuric acid (2.5 ml) and fuming nitric acid (S.G. 1.52) (2.5 ml) was stirred at 0-10° (ice-bath) and treated in portions with 7-chloro-1-hydroxy-3-methylquinazoline-2,4(1H,3H)-dione (103) (1.1 g, 0.005 mol) at such a rate that the temperature of the exothermic reaction was <70°. The mixture was then heated at 100° (water bath) for 1h, the resulting solution cooled (ice-water bath) and treated with crushed ice (10.0 g) to give a yellow solid which was stirred as a suspension in saturated aqueous sodium hydrogen carbonate solution (5.0 ml) for a few min. The resulting solution was acidified with concentrated hydrochloric acid to give 7-chloro-1-hydroxy-3-methyl-6-nitro-8-nitrosoquinazoline-2,4(1H,3H)-dione (104) (0.33 g; 22%) which formed colourless crystals m.p. 264-266 (decomp.) (from ethanol-dimethylformamide), ν_{\max} 3200-2700 br (OH), 1730 and

1670 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.75 (1H, s, H-5) and 3.26 (3H, s, NCH_3).

Found: C, 36.2; H, 1.8; N, 18.2%; M^+ , 302 and 300.
 $\text{C}_9\text{H}_5\text{ClN}_4\text{O}_6$ requires: C, 36.0; H, 1.7; N, 18.6%; M, 302 and 300.

Workup of the aqueous mother liquors gave no further identifiable material.

2,4-Dinitro- α -phenylacetanilide (119b)

2,4-Dinitro- α -phenylacetanilide (119b) was prepared (yield quantitative) by the condensation of 2,4-dinitroaniline with phenylacetyl chloride as described by Mason and Tennant,¹⁶⁶ and had m.p. 105-110° (lit.,¹⁶⁶ 110-112°).

6-Nitro-3-phenylquinoxalin-2(1H)-one 4-N-Oxide (120b)

6-Nitro-3-phenylquinoxalin-2(1H)-one 4-N-oxide (120b) was prepared (yield 80%) by heating 2,4-dinitro- α -phenylacetanilide (119b) with potassium hydroxide in aqueous pyridine as described by Mason and Tennant,¹⁶⁶ and had m.p. 264-267° (lit.,¹⁶⁶ 275-278°).

5-Chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b)

(a) A solution of 6-nitro-3-phenylquinoxalin-2(1H)-one 4-N-oxide (120b) (60.8 g, 0.215 mol) in acetyl chloride (375 ml) and glacial acetic acid (225 ml) was heated under reflux for 24h. The suspension obtained was evaporated and the residue triturated with ether to give a brown solid. This was heated under reflux with ethanol and hot filtered to afford 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) (45.9 g; 71%), which formed yellow-brown crystals m.p. 254-

255° (decomp.) (from glacial acetic acid), ν_{\max} 3200-2700
br (NH/OH), 1670 (CO) and 1530 and 1345 (NO_2) cm^{-1} , $\delta[(\text{CD}_3)_2\text{-SO}]$ 8.46-8.28 (2H, m, ArH), 8.09 (1H, d, $J_{10\text{Hz}}$, ArH), 7.64-
7.40 (3H, m, ArH) and 7.35 (1H, d, $J_{10\text{Hz}}$, ArH).

Found: M^+ , 301.0254.

$\text{C}_{14}\text{H}_8^{35}\text{ClN}_3\text{O}_3$ requires: M, 301.0254.

Found: M^+ , 303.0223.

$\text{C}_{14}\text{H}_8^{37}\text{ClN}_3\text{O}_3$ requires: M, 303.0225.

The combined ethereal and ethanolic liquors were evaporated and the gummy solid was subjected to flash-chromatography over silica.

Elution with cyclohexane-methylene chloride (2:3) afforded a yellow solid which was crystallised from ethanol to give N-acetyl-2,4-dinitroaniline m.p. 120-122° (lit.,¹⁶⁷ 144-146°), ν_{\max} 3340 (NH), 1710 (CO) and 1500 and 1350 (NO_2) cm^{-1} , $\delta(\text{CDCl}_3)$ 10.57 (1H, brs, NH), 9.08 (1H, d, $J_{2.7\text{Hz}}$, H-3), 9.06 (1H, d, $J_{9.4\text{Hz}}$, H-6), 8.43 (1H, dd, $J_{\text{ortho}} 9.4\text{Hz}$, $J_{\text{meta}} 2.7\text{Hz}$, H-5) and 2.35 (3H, s, COCH_3).

Found: C, 42.8; H, 3.1; N, 18.8%; M^+ , 225.

Calc. for $\text{C}_8\text{H}_7\text{N}_3\text{O}_5$: C, 42.7; H, 3.1; N, 18.7%; M, 225.

Further elution with cyclohexane-methylene chloride (2:3) afforded a brown solid which was crystallised from ethanol-glacial acetic acid to give N,N-diacetyl-2,4-dinitroaniline, m.p. 113-114° (lit.,¹⁶⁸ 112-113°), ν_{\max} 1738 and 1695 (CO) and 1540 and 1350 (NO_2) cm^{-1} , $\delta(\text{CDCl}_3)$ 8.96 (1H, d, $J_{2.6\text{Hz}}$, H-3), 8.57 (1H, dd, $J_{\text{ortho}} 8.6\text{Hz}$, $J_{\text{meta}} 2.6\text{Hz}$, H-5), 7.57 (1H, d, $J_{8.6\text{Hz}}$, H-6) and 2.32 (6H, s, COCH_3).

Found: C, 45.0; H, 3.3; N, 15.5%; M^+ , 267.

Calc. for $C_{10}H_9N_3O_6$: C, 45.0; H, 3.4; N, 15.7%; M , 267.

(b) A suspension of 6-nitro-3-phenylquinoxalin-2(1H)-one 4-N-oxide (120b) (0.57 g, 0.002 mol) in propionic acid (3.5 ml) and propionyl chloride (6.0 ml) was heated under reflux for 24h. The resulting suspension was filtered to give 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) (0.10 g; 17%) m.p. 264-267° (decomp.) identical (m.p. and i.r. and 1H n.m.r. spectra) to an authentic sample.

The filtrate was evaporated to give a grey-brown solid (0.58 g) whose t.l.c. in toluene over silica showed it to be a multicomponent mixture which was not further investigated.

(c) A solution of 6-nitro-3-phenylquinoxalin-2(1H)-one 4-N-oxide (120b) (0.57 g, 0.002 mol) and toluene-p-sulphonyl chloride (0.42 g, 0.0022 mol) in dry dimethylformamide (10.0 ml) was heated at 100° (water bath) for 1h. The mixture was evaporated and the residue was treated with water (10.0 ml) to give impure unreacted quinoxalinone (120b) (0.46 g; 81%) m.p. 225-230° (decomp.) identical (i.r. spectrum) to an authentic sample.

The aqueous liquor was extracted with methylene chloride to give a yellow gum (0.18 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture, which was not further investigated.

(d) A suspension of 6-nitro-3-phenylquinoxalin-2(1H)-one 4-N-oxide (120b) (0.57 g, 0.002 mol) in acetic anhydride (6.0 ml) and glacial acetic acid (3.0 ml) was treated dropwise with stirring at 0-10° (ice-bath) with an ice-cold solution of 70%

w/v aqueous perchloric acid (0.6 ml) in acetic anhydride (2.0 ml) and the mixture was stirred at 0-10° for 1h. The resulting solution was poured into dry ether (50.0 ml) to give a brown gum. The ether was decanted and the gum treated with absolute ethanol (20.0 ml) and heated gently at 100° (water bath) for 10 min. Methylene chloride (50.0 ml) was added to the resulting suspension, followed by saturated aqueous sodium hydrogen carbonate solution (25.0 ml) and the three-phase mixture obtained was filtered to remove inorganic material. Evaporation of the methylene chloride phase gave the impure unreacted quinoxalinone N-oxide (120b) (0.41 g; 72%) m.p. 215-218° (decomp.) identical (i.r. spectrum) to an authentic sample.

The ethereal liquor was washed with saturated aqueous sodium hydrogen carbonate solution (3x25.0 ml) and evaporated to give a brown gum (0.13 g) whose t.l.c. in methylene chloride over silica showed it to be a complex mixture, which was not further investigated.

The Attempted Reaction of 2,4-Dinitro-N-methylaniline (53b) with Phenylacetyl Chloride

(a) A solution of 2,4-dinitro-N-methylaniline (53b) (3.9 g, 0.02 mol) in dry benzene (50.0 ml) was treated with phenylacetyl chloride (3.4 g, 0.022 mol) and the mixture was heated under reflux for 24h. The solution was cooled, the solid collected and combined with a second crop obtained by evaporating the benzene filtrate, treating the residue with saturated aqueous sodium hydrogen carbonate and extracting with methylene chloride (3x50 ml), to give unreacted 2,4-dinitro-N-methylaniline (53b) (3.7 g; 94%) m.p. 175-179°, identical (m.p. and

i.r. spectrum) to an authentic sample.

(b) A vigorously stirred suspension of sodium hydride (0.14 g, 0.0055 mol) in dry dimethylformamide (2.0 ml) was treated with a slurry of 2,4-dinitro-N-methylaniline (53b) (0.99 g, 0.005 mol) in dry dimethylformamide (5.0 ml) and the mixture was stirred at room temperature for 0.5h, then a solution of phenylacetyl chloride (0.86 g, 0.0055 mol) in dry dimethylformamide (2.0 ml) was added dropwise and the mixture was stirred at room temperature for 16h. The resulting solution was diluted with water (20.0 ml) to give a solid which was crystallised from glacial acetic acid to afford unreacted 2,4-dinitro-N-methylaniline (53b) (0.59 g; 60%) m.p. 169-172°, identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the glacial acetic acid mother liquor gave a brown gum (0.63 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture, which was not further investigated.

The aqueous liquor was extracted with methylene chloride to give a brown oil (0.31 g) whose t.l.c. in methylene chloride over silica showed it to be a complex mixture, which was not further investigated.

1-Methyl-6-nitro-3-phenylquinoxalin-2(1H)-one 4-N-oxide (147)

A suspension of 6-nitro-3-phenylquinoxalin-2(1H)-one 4-N-oxide (120b) (28.3 g, 0.01 mol) and anhydrous potassium carbonate (75.0 g) in Analar acetone (500 ml) was treated with dimethyl sulphate (34.0 ml, 0.4 mol) and the mixture was heated under reflux for 4h. The resulting suspension was

evaporated and the residue treated with water (300 ml) and extracted with methylene chloride to give a three-phase system which was filtered. The solid so obtained was heated under reflux with water and the insoluble material combined with a second crop of solid obtained by evaporating the methylene chloride extract, followed by crystallisation from ethanol-glacial acetic acid to give 1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one 4-N-oxide (147) (24.2 g; 81%) m.p. 185-190° (decomp.) (lit.,¹⁶⁶ 207-208°).

The Reaction of 1-Methyl-6-nitro-3-phenylquinoxalin-2(1H)-one 4-N-oxide (147) with Acetyl Chloride

A suspension of 1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one 4-N-oxide (147) (0.6 g, 0.002 mol) in a mixture of glacial acetic acid (3.0 ml) and acetyl chloride (5.0 ml) was heated under reflux for 7h. The solution obtained was evaporated and the residue triturated with ether-toluene to give a solid mixture of 7-chloro-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (148) and 5-chloro-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (149) (0.33 g; 54%) m.p. 195-205°, $\delta[(\text{CD}_3)_2\text{SO}]$ (49°) 8.44 (1H, s, ArH), 8.38-8.12 (4H, m, ArH), 8.18 (1H, d, J10Hz, ArH), 7.82 (1H, s, ArH), 7.64 (1H, d, J10Hz, ArH), 7.58-7.43 (6H, m, ArH) and 3.66 (6H, s, NCH_3), whose t.l.c. in ethyl acetate over silica showed it to be unresolvable on a preparative scale.

The Attempted Reaction of 1-Methyl-6-nitro-3-phenylquinoxalin-2(1H)-one 4-N-oxide (147) with Toluene-p-sulphonyl chloride

A solution of 1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one 4-N-oxide (147) (0.59 g, 0.002 mol) and toluene-p-sulphonyl chloride (0.42 g, 0.0022 mol) in dry dimethylformamide (10.0 ml) was heated at 100° (water bath) for 1h. The resulting mixture was evaporated and the residue treated with water (10.0 ml) to give a yellow solid which was crystallised from ethanol-glacial acetic acid to give the unreacted quinoxalinone N-oxide (147) (0.24 g; 41%) m.p. 195-200 (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the ethanol-acetic acid mother liquor gave a brown gum (0.4 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture, which was not further investigated.

The Reaction of 1-Methyl-6-nitro-3-phenylquinoxalin-2(1H)-one 4-N-Oxide (147) with Acetic Anhydride in the Presence of Perchloric Acid

A suspension of 1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one 4-N-oxide (147) (0.59 g, 0.002 mol) in acetic anhydride (6.0 ml) and glacial acetic acid (3.0 ml) was stirred and treated dropwise at 0-10° (ice-bath) with an ice-cold solution of 70% w/v aqueous perchloric acid (0.6 ml) in acetic anhydride (2.0 ml) and the mixture was stirred at 0-10° for 1h. The resulting solution was stored in a refrigerator overnight, then allowed to warm up to room temperature. The precipitated solid was collected to give 4-acetoxy-1-methyl-6-nitro-2-oxo-3-phenylquinoxalinium perchlorate (150) (0.60 g; 73%) m.p. 90-

95°, ν_{\max} 1715 (CO) cm^{-1} , which was immediately reacted with concentrated hydrochloric acid as described below.

The acetic anhydride-acetic acid mother liquor was poured into dry diethyl ether (50.0 ml) to give 7-acetoxy-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (151) (0.11 g; 16%) which formed brown needles m.p. 194-195° (from ethanol), ν_{\max} 1770 and 1670 (CO) and 1515 and 1340 (NO_2) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.61 (1H, s, ArH), 8.27-8.22 (2H, m, ArH), 7.71 (1H, s, ArH), 7.56-7.52 (3H, m, ArH), 3.31 (3H, s, NCH_3) and 2.41 (3H, s, CH_3).

Found: C, 60.1; H, 3.7; N, 12.3%; M^+ , 339.

$\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}_5$ requires: C, 60.2; H, 3.9; N, 12.4%; M, 339.

The ethereal liquor was washed with saturated aqueous sodium hydrogen carbonate solution (50.0 ml) and evaporated to give a brown gum (0.2 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture, which was not further investigated.

The Reaction of 4-Acetoxy-1-methyl-6-nitro-2-oxo-3-phenylquinoxalinium Perchlorate (150) with Concentrated Hydrochloric Acid

The crude 4-acetoxy-1,2-dihydro-1-methyl-6-nitro-2-oxo-3-phenylquinoxalinium perchlorate (150) (0.60 g, 0.00145 mol) prepared as described above was added in portions with stirring at 0-10° (ice-bath) to concentrated hydrochloric acid (5.0 ml) and the mixture stirred at 0-10° for 1h. The resulting solution was diluted with water (15.0 ml) and the precipitated solid collected to afford 1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one 4-N-oxide (147) (0.46 g; 100%) m.p. 175-180°, identical (m.p. and i.r. spectrum) to an authentic sample.

5-Chloro-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (149)

(a) A suspension of 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) (6.0 g, 0.02 mol) and anhydrous potassium carbonate (15.0 g) in Analar acetone (500 ml) was treated with dimethyl sulphate (10.0 ml) and the mixture was heated under reflux for 4h. The mixture was evaporated and the residue treated with water (100 ml) and ethyl acetate (200 ml). The resulting three-phase system was filtered to give a brown solid which was treated with boiling water (20.0 ml) and hot filtered to give 5-chloro-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (149) (1.97 g; 31%) which formed yellow cubes m.p. 224-225° (from ethanol-glacial acetic acid), ν_{\max} 1665 (CO) and 1530 and 1345 (NO₂) cm⁻¹, δ [(CD₃)₂SO] 8.44-8.28 (2H, m, ArH), 8.18 (1H, d, J10Hz, ArH), 7.65 (1H, d, J10Hz, ArH), 7.60-7.42 (3H, m, ArH), and 3.70 (3H, s, NCH₃).

Found: C, 57.0; H, 3.2; N, 13.2%; M⁺, 317 and 315.

C₁₅H₁₀ClN₃O₃ requires: C, 57.1; H, 3.2; N, 13.3%; M, 317 and 315.

The ethyl acetate mother liquor was evaporated and the residue triturated with ether to give a solid mixture of 5-chloro-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (149) and 5-chloro-2-methoxy-6-nitro-3-phenylquinoxaline (152) (2.9 g; 44%), m.p. 188-192° (decomp.).

The ethereal mother liquor was evaporated and the residue triturated with ethanol to give 5-chloro-2-methoxy-6-nitro-3-phenylquinoxaline (152) (0.3 g; 0.5%) which formed pale yellow needles m.p. 159-160° (from ethanol), ν_{\max} 1565 and 1365 (NO₂) cm⁻¹, δ [(CD₃)₂SO] 8.30-8.06 (3H, m, ArH), 7.93 (1H, d, J10Hz, ArH), 7.64-7.44 (3H, m, ArH) and 4.19 (3H, s, OCH₃).

Found: C, 57.1; H, 3.2; N, 13.1%; M^+ , 317 and 315.
 $C_{15}H_{10}ClN_3O_3$ requires: C, 57.1; H, 3.2; N, 13.3%; M , 317 and 315.

(b) A suspension of 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) (12.0 g, 0.04 mol) in aqueous 2M sodium hydroxide (300 ml) was treated with dimethyl sulphate (40.0 ml) and the mixture shaken mechanically at room temperature for 3h, then treated with a further portion of dimethyl sulphate (4.0 ml) and shaken at room temperature for a further 1h with the addition of aqueous 2M sodium hydroxide solution as necessary to keep the mixture alkaline. The resulting suspension was filtered and the solid washed with water and crystallised from ethanol-glacial acetic acid to give 5-chloro-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (149) (6.3 g; 50%) m.p. 206-210° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The ethanolic filtrate was evaporated to give a brown solid which was subjected to flash chromatography over silica.

Elution with ethyl acetate afforded unreacted 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) (0.65 g; 5%) m.p. 288-292° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

(c) A solution of 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) (6.0 g, 0.02 mol) in dry dimethylformamide (35.0 ml) was added to a vigorously stirred suspension of sodium hydride (0.57 g, 0.024 mol) in dry dimethylformamide (20.0 ml) and the mixture was stirred at room temperature with protection from atmospheric moisture for 15 min. The mixture was then treated with methyl iodide (5.7 g, 0.04 mol)

and stirred at room temperature for a further 24h. The suspension obtained was treated with water (200 ml), the solid collected, washed with water and crystallised from ethanol-glacial acetic acid to give 5-chloro-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (149) (3.7 g; 58%) m.p. 210-214° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The ethanol-glacial acetic acid mother liquor was evaporated to give a gummy solid (1.55 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture, which was not further investigated.

The Attempted Reaction of 5-Chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) with Ammonia

A suspension of 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) (0.6 g, 0.002 mol) in liquid ammonia (25.0 ml) was sealed in an autoclave for 24h. The resulting suspension was allowed to evaporate and the residue treated with water (5.0 ml) to give the unreacted quinoxalinone (122b) (0.59 g; 98%) m.p. 264-268 (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Reaction of 5-Chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) with Toluene-p-sulphonamide

A vigorously stirred suspension of sodium hydride (0.05 g, 0.0022 mol) in dry dimethylformamide (2.0 ml) was treated with a solution of toluene-p-sulphonamide (0.34 g, 0.002 mol) in dry dimethylformamide (2.0 ml) and the suspension stirred at room temperature for 15 min with protection from atmospheric

moisture. A solution of 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) (0.60 g, 0.002 mol) in dry dimethylformamide (5.0 ml) was added dropwise and the resulting mixture stirred at room temperature for 17.5h. Addition of water (20.0 ml) and extraction with methylene chloride (3x25.0 ml) afforded a solid (0.34 g) whose t.l.c. in methylene chloride over silica showed it to be a mixture of the unreacted quinoxalinone (122b) and toluene-p-sulphonamide.

The aqueous alkaline mother liquor was acidified with concentrated hydrochloric acid to give unreacted 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) (0.38 g; 64%) m.p. 264-269° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The acidic aqueous liquor was extracted with methylene chloride to give impure unreacted toluene-p-sulphonamide (0.14 g; 41%) m.p. 118-123°, identical (i.r. spectrum) to an authentic sample.

The Attempted Reaction of 5-Chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) with Diphenylphosphinamide (68)

A vigorously stirred suspension of sodium hydride (0.10 g, 0.004 mol) in dry dimethylformamide (2.0 ml) was treated with a slurry of diphenylphosphinamide (68) (0.43 g, 0.002 mol) in dry dimethylformamide (3.0 ml) and the mixture was stirred at room temperature for 0.5h with protection from atmospheric moisture. A solution of 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) (0.60 g, 0.002 mol) in dry dimethylformamide (5.0 ml) was then added dropwise and the mixture stirred at room temperature for 17h. The resulting

suspension was filtered and the solid obtained heated under reflux with ethanol and hot filtered to give a salt, which was treated with aqueous 2M hydrochloric acid to give a solid tentatively formulated as 5-amino-6-nitro-3-phenylquinoxalin-2(1H)-one (124a) (0.03 g; 5%) m.p. 285-290° (decomp.); ν_{\max} 3200-2700 br (NH/OH) and 1660 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.57-8.44 (2H, m, ArH), 8.12 (1H, d, $J_{9.3\text{Hz}}$, H-7), 7.55-7.46 (3H, m, ArH) and 6.81 (1H, d, $J_{9.3\text{Hz}}$, H-8).

Found: M^+ , 282.0524.

$\text{C}_{14}\text{H}_{10}\text{N}_4\text{O}_3$ requires: M , 282.0753.

Evaporation of the ethanolic filtrate gave impure unreacted diphenylphosphinamide (68) (0.36 g; 83%) m.p. 155° (decomp.) identical (i.r. spectrum) to an authentic sample.

The dimethylformamide mother liquor was diluted with water (20.0 ml) and acidified with concentrated hydrochloric acid to give the unreacted quinoxalinone (122b) (0.47 g; 78%) m.p. 245-250° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Reaction of 5-Chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) with Pyridine in Dimethylformamide

(a) A solution of 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) (0.60 g, 0.002 mol) and Analar pyridine (0.18 g, 0.0022 mol) in dry dimethylformamide (25.0 ml) was stirred at 50° (oil bath) for 24h. The mixture was evaporated to give the unreacted quinoxalinone (122b) as a light brown solid (0.52 g; 87%) m.p. 260-264° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

(b) A solution of 5-chloro-6-nitro-3-phenylquinoxalin-

2(1H)-one (122b) (0.60 g, 0.002 mol) and Analar pyridine (0.18 g, 0.0022 mol) in dry dimethylformamide (25.0 ml) was heated under reflux for 20h. The mixture was evaporated to give a brown solid (0.75 g), which crystallised from ethanol-dimethylformamide to give 5-N,N-dimethylamino-6-nitro-3-phenylquinoxalin-2(1H)-one (138) as orange-yellow crystals m.p. 265-267°, ν_{\max} 3200-2600, br (NH/OH) and 1655 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.38-8.33 (2H, m, ArH), 7.89 (1H, d, J9Hz, H-7), 7.56-7.47 (3H, m, ArH), 6.84 (1H, d, J9Hz, H-8) and 3.10 (6H, s, NCH_3).

Found: C, 61.7; H, 4.4; N, 17.9%; ($M^+ + 1$) 311.

$\text{C}_{16}\text{H}_{14}\text{N}_4\text{O}_3$ requires: C, 61.9; N, 4.6; N, 18.1%; M, 310.

5-Methylamino-6-nitro-3-phenylquinoxalin-2(1H)-one (124d)

A solution of 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) (6.0 g, 0.02 mol) in dry dimethylformamide (25.0 ml) was stirred at 50° (oil bath) and treated with 33% w/v ethanolic methylamine solution (20.0 ml), then with two further portions of 33% w/v ethanolic methylamine solution (20.0 ml) at 4h intervals and the resulting mixture finally stirred at 50° for 17h. The gummy orange solid obtained on evaporation of solvent was boiled with ethanol (20.0 ml) and hot filtered to give an orange solid which was crystallised from toluene-dimethylformamide to give 5-methylamino-6-nitro-3-phenylquinoxalin-2(1H)-one (124d) (3.6 g; 61%) as orange crystals m.p. 304-306° (from glacial acetic acid-dimethylformamide), ν_{\max} 3250 br (NH) and 1660 br (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 7.73 (1H, d, J8.9Hz, H-7), 7.16-7.08 (5H, m, ArH), 6.25 (1H, d, J8.9Hz, H-8) and 4.20 (3H, d, J2.0 Hz, NHCH_3).

Found: C, 60.9; H, 4.1; N, 18.6%; M^+ , 296.

$C_{15}H_{12}N_4O_3$ requires: C, 60.8; H, 4.1; N, 18.9%; M , 296.

The ethanolic filtrate, on cooling, deposited impure unreacted 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) (0.63 g; 11%) m.p. 225-230° (decomp.) identical (i.r. spectrum) to an authentic sample.

The ethanolic filtrate was evaporated to give a brown gum (2.6 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture, which was not further investigated.

5-Methylamino-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one
(174b)

A solution of 5-chloro-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (149) (3.2 g, 0.01 mol) in dry dimethylformamide (50.0 ml) was stirred at 50° (oil bath), treated with 33% w/v ethanolic methylamine solution (10.0 ml) and the mixture heated at 50° for 4h. A further portion of 33% w/v ethanolic methylamine solution (10.0 ml) was then added and heating and stirring at 50° continued for a total of 24h. The resulting solution was evaporated and the residue triturated with ethanol to afford 5-methylamino-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (174b) (2.9 g; 92%) which formed yellow crystals m.p. 242-243° (from ethanol-dimethylformamide), ν_{\max} 3380w and 3260w (NH), 1640 (CO) and 1500 and 1335 (NO_2) cm^{-1} , $\delta(CDCl_3)$ 9.35 (1H, br, NH), 8.33 (1H, d, J10Hz, H-6) 8.32-8.20 (2H, m, ArH), 7.60-7.37 (3H, m, ArH), 6.57 (1H, d, J10Hz, H-7), 3.77 (3H, s, NCH_3) and 3.68 (3H, d, J5Hz, $NHCH_3$).

Found: C, 62.2; H, 4.3; N, 18.3%; M^+ , 310.

$C_{16}H_{14}N_4O_3$ requires: C, 61.9; H, 4.6; N, 18.1%; M , 310.

The ethanolic filtrate was evaporated to give a brown gum (0.86 g) which was subjected to flash-chromatography over silica.

Elution with cyclohexane-methylene chloride (1:1) afforded an orange solid tentatively formulated as 5-methylamino-2-methoxy-6-nitro-3-phenylquinoxaline (0.01 g; 0.5%) m.p. 171-175°, ν_{\max} 3250 (NH) and 1495 and 1340 (NO_2) cm^{-1} , $\delta(\text{CDCl}_3)$ 9.75 (1H, br, NH), 8.28 (1H, d, $J_{10\text{Hz}}$, H-6), 8.09-7.97 (2H, m, ArH), 7.49-7.39 (3H, m, ArH), 6.89 (1H, d, $J_{10\text{Hz}}$, H-7), 4.10 (3H, s, OCH_3) and 3.69 (3H, d, $J_{5.5\text{Hz}}$, NHCH_3).

Further elution with methylene chloride through to ethanol afforded a series of intractable gums and glasses (total 0.69 g) which were not further investigated.

5-Benzylamino-6-nitro-3-phenylquinoxalin-2(1H)-one (141a)

A solution of 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) (12.0 g, 0.04 mol) and benzylamine (8.6 g, 0.08 mol) in dry dimethylformamide (75.0 ml) was stirred at 50° (oil bath) for 24h. The suspension obtained was evaporated and the residue triturated with ethanol to give a yellow solid which was combined with a second crop obtained by triturating the brown gum obtained by evaporating the ethanolic mother liquor with ether, to give 5-benzylamino-6-nitro-3-phenylquinoxalin-2(1H)-one (141a) (8.8 g; 60%) as yellow crystals m.p. 245-246° (decomp.) (from ethanol-dimethylformamide), ν_{\max} 3240w (NH), 1660 (CO) and 1500 and 1300 (NO_2) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ (64°) 9.52-9.34 (1H, m, NH) (collapses to brs, δ 9.52 on irradiation at δ 4.35), 8.20-8.11 (2H, m, ArH), 8.21 (1H, d, $J_{10\text{Hz}}$, H-7) (collapses to s, δ 8.20 on irradiation at δ 5.65),

7.52-7.28 (8H, m, ArH), 5.65 (1H, d, J10Hz, H-8) (collapses to s, δ 5.62 on irradiation at δ 8.21) and 4.35 (2H, d, J6Hz, CH₂) (collapses to s, δ 4.34 on irradiation at δ 9.52).

Found: C, 67.7; H, 4.3; N, 15.1%; M⁺, 372.

C₂₁H₁₆N₄O₃ requires: C, 67.4; H, 4.3; N, 15.6%; M, 372.

The combined ethanolic and ethereal mother liquors were evaporated to afford a gummy solid (3.7 g) whose t.l.c. in methylene chloride over silica showed it to be a multi-component mixture, which was not further investigated.

5-Benzylamino-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one
(153)

A solution of 5-chloro-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (149) (3.2 g, 0.01 mol) and benzylamine (2.1 g, 0.02 mol) in dry dimethylformamide (50.0 ml) was stirred at 50° (oil bath) for 24h. The mixture was evaporated and the residue was triturated with ethanol to give 5-benzylamino-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (153) (3.2 g; 82%) which formed orange-yellow needles m.p. 218-219° (from ethanol-dimethylformamide), ν_{\max} 3260 (NH), 1640 (CO) and 1500w and 1320w (NO₂) cm⁻¹, δ [(CD₃)₂SO] 9.40 (1H, br, NH), 8.35 (1H, d, J10Hz, H-7), 8.25-8.20 (2H, m, ArH), 7.47-7.32 (8H, m, ArH), 6.93 (1H, d, J10Hz, H-8), 5.40 (2H, d, J4Hz, CH₂) and 3.80 (3H, s, NCH₃).

Found: C, 68.5; H, 4.7; N, 14.8%; M⁺, 386.

C₂₂H₁₈N₄O₃ requires: C, 68.4; H, 4.7; N, 14.5%; M, 386.

5-(N-Benzyl,N-methyl)amino-6-nitro-3-phenylquinoxalin-2(1H)-one (141b)

A solution of 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-

one (122b) (0.60 g, 0.002 mol) and N-benzylmethylamine (0.49 g, 0.004 mol) in dry dimethylformamide (25.0 ml) was stirred at 50° (oil bath) for 24h. The resulting solution was evaporated and the residue crystallised from ethanol to give 5-(N-benzyl,N-methyl)amino-6-nitro-3-phenylquinoxalin-2(1H)-one (141b) (0.47 g; 62%) which formed yellow crystals m.p. 195-196° (from ethanol), ν_{\max} 3200-2600 br (NH/OH), 1665 (CO), 1645 (C=N) and 1530 and 1330 (NO₂) cm⁻¹, $\delta[(\text{CD}_3)_2\text{SO}]$ 12.79 (1H, br s, NH), 8.33-8.23 (2H, m, ArH), 7.92 (1H, d, J9Hz, ArH), 7.49-7.31 (8H, m, ArH), 7.02 (1H, d, J9Hz, ArH), 4.59 (2H, s, CH₂) and 2.88 (3H, s, NCH₃).

Found: C, 68.3; H, 4.6; N, 14.6%; (M⁺-1), 385.

C₂₂H₁₈N₄O₃ requires: C, 68.4; H, 4.7; N, 14.5%; M, 386.

The ethanolic filtrate was evaporated to give an orange gum (0.38 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture, which was not further investigated.

The Attempted Reaction of 5-Chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) with Dibenzylamine

A solution of 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) (0.60 g, 0.002 mol) and dibenzylamine (0.79 g, 0.004 mol) in dry dimethylformamide (25.0 ml) was stirred at 50° (oil bath) for 24h. The mixture was evaporated and the residue triturated with ether to give an intractable solid (0.63 g) m.p. 165-170° (decomp.) whose t.l.c. in ethyl acetate over silica showed it to be a close running multicomponent mixture from which no identifiable material could be obtained.

The ethereal mother liquor was evaporated to give a brown

oil (0.73 g) whose t.l.c. in methylene chloride over silica showed it to be a complex mixture which was not further investigated.

The Attempted Reaction of 5-Methylamino-6-nitro-3-phenylquinoxalin-2(1H)-one (124d) with Formaldehyde and Sodium Cyanide in the Presence of Zinc Chloride

A suspension of 5-methylamino-6-nitro-3-phenylquinoxalin-2(1H)-one (124d) (0.59 g, 0.002 mol), paraformaldehyde (0.18 g, 0.006 mol), powdered anhydrous zinc chloride (2.0 g, 0.015 mol) and sodium cyanide (0.3 g, 0.006 mol) in glacial acetic acid (5.0 ml) and dry dimethylformamide (6.0 ml) was stirred at 50° (oil bath) for 6h. The resulting suspension was treated with hot water (10.0 ml) and filtered to give the unreacted quinoxalinone (124d) (0.47 g; 80%) m.p. 295-299° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous mother liquor was extracted with methylene chloride to give an orange oil (0.51 g) whose t.l.c. in ethyl acetate showed it to be a multicomponent mixture, which was not further investigated.

2,8-Diphenyl-3-hydroxy-3H-imidazo[4,5-f]quinoxalin-7(6H)-one (142)

5-Benzylamino-6-nitro-3-phenylquinoxalin-2(1H)-one (141a) (4.1 g, 0.011 mol) was added to a solution of sodium hydroxide (2.2 g, 0.055 mol) in methanol (60.0 ml) and the mixture was heated under reflux for 5h. The resulting mixture was evaporated, the residue treated with water (20.0 ml) and the solution acidified with concentrated hydrochloric acid to

give a yellow solid which was crystallised from glacial acetic acid-dimethylformamide to afford

2,8-diphenyl-3-hydroxy-3H-imidazo[4,5-f]quinoxalin-7(6H)-one (142) (4.4 g; 94%) as yellow crystals m.p. 258-260° (decomp.) (from glacial acetic acid-dimethylformamide), ν_{\max} 3400 br, w, (NH/OH) and 1660 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 10.15 (1H, brs, NH), 8.55-8.50 (2H, m, ArH), 8.33-8.28 (2H, m, ArH), 7.90 (1H, d, J9Hz, ArH), 7.68-7.65 (3H, m, ArH) and 7.53-7.47 (4H, m, ArH).

Found: M^+ , 354.0918.

$\text{C}_{21}\text{H}_{14}\text{N}_4\text{O}_2$ requires: M , 354.1117.

The Attempted Methylation of 2,8-Diphenyl-3-hydroxy-3H-imidazo[4,5-f]quinoxalin-7(6H)-one (142)

A solution of 2,8-diphenyl-3-hydroxy-3H-imidazo[4,5-f]quinoxalin-7(6H)-one (142) (0.35 g, 0.001 mol) in aqueous 2M sodium hydroxide (5.0 ml) was treated dropwise with dimethyl sulphate (1.0 ml) and the mixture was mechanically shaken at room temperature for 1h. The mixture was acidified with concentrated hydrochloric acid and extracted with methylene chloride to give an intractable brown gum (0.51 g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture from which no identifiable material could be obtained.

The Reaction of 2,8-Diphenyl-3-hydroxy-3H-imidazo[4,5-f]quinoxalin-7(6H)-one (142) with Acetic Anhydride

A suspension of 2,8-diphenyl-3-hydroxy-3H-imidazo[4,5-f]quinoxalin-7(6H)-one (142) (0.09 g, 0.00025 mol) in acetic anhydride (1.5 ml) was heated under reflux for several min.

The resulting suspension was cooled and filtered to give 3-acetoxy-2,8-diphenyl-3H-imidazo[4,5-f]quinoxalin-7(6H)-one (144a) (0.07 g; 71%) m.p. 262-265°, ν_{max} 3150 to 2500 br, w (NH/OH) and 1810 and 1660 (CO) cm^{-1} , which on attempted crystallisation from ethanol-dimethylformamide was reconverted into the impure starting N-hydroxyimidazoquinoxalinone (142) m.p. 210-215° (decomp.) identical (i.r. spectrum) to an authentic sample.

The Attempted Reaction of 2,8-Diphenyl-3-hydroxy-3H-imidazo[4,5-f]quinoxalin-7(6H)-one (142) with Phenyl Isocyanate

A solution of 2,8-diphenyl-3-hydroxy-3H-imidazo[4,5-f]quinoxalin-7(6H)-one (142) (0.43 g, 0.001 mol) in dry dimethylformamide (25.0 ml) was treated with phenyl isocyanate (0.12 g, 0.001 mol) and the mixture left at room temperature for 24h. The mixture was then evaporated to give an orange solid (0.47 g) m.p. 170-175° (decomp.) whose t.l.c. in ether over silica showed it to be a multicomponent mixture from which no identifiable material was obtained.

2,8-Diphenyl-3H-imidazo[4,5-f]quinoxalin-7(6H)-one (145)

A solution of 2,8-diphenyl-3-hydroxy-3H-imidazo[4,5-f]quinoxalin-7(6H)-one (142) (0.86 g, 0.024 mol) in 70% v/v aqueous dimethylformamide (20.0 ml) was treated with sodium dithionate (0.86 g) and the suspension was heated under reflux for 1h then treated with a further portion of sodium dithionate (0.86 g) and heating under reflux continued for a further 1h. The resulting suspension was hot filtered to remove inorganic material and the solid which separated from the filtrate on

cooling was combined with further material obtained by evaporating the aqueous dimethylformamide mother liquor, dissolution of the solid residue in water (10.0 ml), and acidification of the aqueous solution with concentrated hydrochloric acid to afford 2,8-diphenyl-3H-imidazo[4,5-f]-quinoxalin-7(6H)-one (145) (total 0.80 g; 98%) which formed yellow needles m.p. 334-335 (decomp.) (from dimethylformamide-water), ν_{\max} 3600-3200 br, w, (NH/OH) and 1645 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.72-8.45 (2H, m, ArH), 8.42-8.23 (2H, m, ArH), 7.85 (1H, d, J8Hz, ArH), 7.68-7.44 (6H, m, ArH) and 7.24 (1H, d, J8Hz, ArH).

Found: 338.1165.

$\text{C}_{21}\text{H}_{14}\text{N}_4\text{O}$ requires: 338.1168.

2,8-Diphenyl-3-hydroxy-6-methyl-3H-imidazo[4,5-f]quinoxalin-7(6H)-one (154)

(a) A stirred suspension of 5-benzylamino-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (153) (0.39 g, 0.001 mol) in Analar pyridine (5.0 ml) at 100° (water bath) was treated with 20% w/v aqueous potassium hydroxide (5.0 ml) and the mixture stirred at 100° for 1h. The solution obtained was diluted with water (5.0 ml) and the precipitated solid was collected to give the unreacted quinoxalinone (153) (0.03 g; 8%) m.p. 205-208° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous pyridine mother liquor was acidified with concentrated hydrochloric acid to give 2,8-diphenyl-3-hydroxy-6-methyl-3H-imidazo[4,5-f]quinoxalin-7(6H)-one (154) (0.31 g; 91%) which formed yellow crystals m.p. 205-207° (decomp.)

(from glacial acetic acid), ν_{\max} 3400-2600 br (OH) and 1635 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.45-8.41 (2H, m, ArH), 8.33-8.28 (2H, m, ArH), 7.92 (1H, d, J_{9Hz} , H-5), 7.66-7.51 (7H, m, ArH) and 3.78 (3H, s, NCH_3).

Found: M^+ , 368.1436.

$\text{C}_{22}\text{H}_{16}\text{N}_4\text{O}_2$ requires: M , 368.1444.

(b) A solution of 5-benzylamino-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (153) (0.39 g, 0.001 mol) in methanol (5.0 ml) was treated with a solution of sodium hydroxide (0.2 g, 0.005 mol) in methanol (4.0 ml) and the mixture was heated under reflux for 5h. The resulting suspension was evaporated and the residue treated with water (10.0 ml) and acidified with concentrated hydrochloric acid to give the unreacted quinoxalinone (153) (0.27 g; 69%) m.p. 194-198°, identical (m.p. and i.r.spectrum) to an authentic sample.

The Attempted Base-catalysed Cyclisation of 5-(N-Benzyl,N-methyl)amino-6-nitro-3-phenylquinoxalin-7(6H)-one (141b)

(a) A stirred solution of 5-(N-benzyl,N-methyl)amino-6-nitro-3-phenylquinoxalin-7(6H)-one (141b) (0.39 g, 0.001 mol) in Analar pyridine (10.0 ml) was heated at 100° (water bath), treated with 20% w/v aqueous potassium hydroxide (10.0 ml), and the mixture maintained at 100° for 1h. Dilution with water (10.0 ml) followed by acidification with concentrated hydrochloric acid gave the unreacted quinoxalinone (141b) (0.37 g, 95%) m.p. 185-190°, identical (m.p. and i.r. spectrum) to an authentic sample.

(b) 5-(N-Benzyl,N-methyl)amino-6-nitro-3-phenylquinoxalin-

7(6H)-one (141b) (0.77 g, 0.002 mol) was treated with a solution of sodium hydroxide (0.4 g, 0.01 mol) in methanol (20.0 ml) and the mixture was heated under reflux for 5h. The mixture was evaporated, the residue treated with water (15.0 ml), and extracted with methylene chloride to give the impure unreacted quinoxalinone (141b) (0.73 g; 95%) m.p. 160-165°, identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Reaction of 5-Chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) with Hydrazine Monohydrate

A solution of 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) (0.60 g, 0.002 mol) and 100% hydrazine monohydrate (0.3 ml, 0.006 mol) in dimethylformamide (5.0 ml) was heated under reflux for 1h. The mixture was evaporated and the resulting residue triturated with ethanol to give a brown solid which was crystallised from ethanol-glacial acetic acid with clarification with animal charcoal to afford impure 5-N,N-dimethylamino-6-nitro-3-phenylquinoxalin-2(1H)-one (138) (0.39 g; 63%) m.p. 200-203°, identical (i.r. spectrum) to an authentic sample.

Evaporation of the ethanolic mother liquor gave a brown gum (0.69 g) whose t.l.c. in ether over silica showed it to be a close-running multicomponent mixture from which no identifiable material could be obtained.

The Attempted Reaction of 5-Chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) with Phenylhydrazine

(a) A solution of 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) (0.60 g, 0.002 mol) and phenylhydrazine

(0.22 g, 0.002 mol) in dry dimethylformamide (25.0 ml) was stirred at 50° (oil bath) for 70h. The mixture was evaporated and the residue triturated with toluene to give the unreacted quinoxalinone (122b) (0.52 g; 87%) m.p. 248-250°, identical (m.p. and i.r. spectrum) to an authentic sample.

The toluene mother liquor was evaporated to give a red-brown gum (0.25 g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture, which was not further investigated.

(b) A solution of 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) (0.60 g, 0.002 mol) and phenylhydrazine (0.22 g, 0.002 mol) in dry dimethylformamide (25.0 ml) was heated under reflux for 1h. The resulting solution was evaporated to give an intractable brown gum (0.81 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture which resisted further purification.

5-(N-Methyl,N-phenylacetamido)-6-nitro-3-phenylquinoxalin-2(1H)-one (175a)

A solution of 5-methylamino-6-nitro-3-phenylquinoxalin-2(1H)-one (124d) (1.8 g, 0.006 mol) and phenylacetyl chloride (1.0 g, 0.0066 mol) in dry dimethylformamide (15.0 ml) was heated at 100° (water bath) for 1h. The mixture was evaporated and the residue crystallised from ethanol-dimethylformamide to give a yellow solid which was combined with a second crop obtained by triturating the residue, obtained on evaporation of the ethanolic filtrate, with ethanol to afford 5-(N-methyl,N-phenylacetamido)-6-nitro-3-phenylquinoxalin-

2(1H)-one (175a) (2.3 g; 91%) which formed yellow crystals m.p. 272-273° (from ethanol-dimethylformamide), ν_{\max} 3200-2700, br (NH/OH), 1680 and 1645 (CO) and 1525 and 1335 (NO₂) cm⁻¹, $\delta[(\text{CD}_3)_2\text{SO}]$ 8.49-8.37 (2H, m, ArH), 8.27 (1H, d, J9.5Hz, H-7), 7.64 (1H, d, J9.5Hz, H-8), 7.55-7.35 (3H, m, ArH), 6.99-6.93 (5H, m, ArH), 3.40 (2H, s, CH₂) and 3.30 (3H, s, NCH₃).

Found: C, 66.4; H, 4.4; N, 13.5%; M⁺, 414.

C₂₃H₁₈N₄O₄ requires: C, 66.7; H, 4.4; N, 13.5%; M, 414.

1-Methyl-5-(N-methyl,N-phenylacetamido)-6-nitro-3-phenylquinoxalin-2(1H)-one (175b)

A solution of 5-methylamino-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (174b) (1.9 g, 0.006 mol) in dry dimethylformamide (50.0 ml) was heated at 100° (water bath) and treated with phenylacetyl chloride (1.0 g, 0.0066 mol) and the mixture was heated at 100° for 1h. The solution obtained was evaporated and the resultant solid residue crystallised to afford 1-methyl-5-(N-methyl,N-phenylacetamido)-6-nitro-3-phenylquinoxalin-2(1H)-one (175b) (1.8 g; 70%) which formed orange-yellow cubes m.p. 247-248° (from ethanol-dimethylformamide), ν_{\max} 1660 br (CO) cm⁻¹, $\delta[(\text{CD}_3)_2\text{SO}]$ 8.35 (1H, d, J9.5Hz, H-7), 8.29-8.14 (2H, m, ArH), 7.84 (1H, d, J9.5Hz, H-8), 7.77-6.77 (8H, m, ArH) 3.74 (3H, s, NCH₃), 3.67 (1H, s, CH₂), 3.52 (1H, s, CH₂) and 3.18 (3H, s, NCH₃).

Found: C, 66.9; H, 4.7; N, 13.3%; M⁺, 428.

C₂₄H₂₀N₄O₄ requires: C, 67.3; H, 4.7; N, 13.1%; M, 428.

The ethanol-dimethylformamide mother liquor was evaporated to give a red-brown gum (1.0 g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture, which was not further investigated.

5-(N-Benzyl,N-phenylacetamido)-6-nitro-3-phenylquinoxalin-2(1H)-one (175c)

A solution of 5-benzylamino-6-nitro-3-phenylquinoxalin-2(1H)-one (141a) (3.0 g, 0.008 mol) and phenylacetyl chloride (1.4 g, 0.0088 mol) in dry dimethylformamide (40.0 ml) was heated at 100° for 3h. The resulting solution was evaporated and the residue was stirred with saturated aqueous sodium hydrogen carbonate solution (50.0 ml) at room temperature for 0.5h. The suspension was filtered and the solid obtained crystallised from ethanol-dimethylformamide and combined with a second crop obtained by evaporating the ethanolic filtrate, to afford 5-(N-benzyl,N-phenylacetamido)-6-nitro-3-phenylquinoxalin-2(1H)-one (175c) (3.6 g; 91%) which formed colourless crystals m.p. 248-249° (from ethanol-glacial acetic acid), ν_{\max} 3570 br (NH/OH), 1690 and 1645 (CO) and 1520 and 1340 (NO₂) cm⁻¹, δ [(CD₃)₂SO] 8.20-8.11 (3H, m, ArH), 7.56-7.42 (4H, m, ArH), 7.10-6.90 (10H, m, ArH), 5.07 (1H, d, J14Hz, CH₂), 4.59 (1H, d, J14Hz, CH₂) and 3.46 (1H, s, CH₂).

Found: C, 71.2; H, 4.5; N, 11.7%; M⁺, 490.

C₂₉H₂₂N₄O₄ requires: C, 71.0; H, 4.5; N, 11.4%; M, 490.

5-(N-Benzyl,N-phenylacetamido)-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (175d)

A solution of 5-benzylamino-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (153) (1.9 g, 0.005 mol) in dry dimethylformamide (35.0 ml) was treated with phenacetyl chloride (0.85 g, 0.0055 mol) and the mixture was heated at 100° (water bath) for 3h. The resulting solution was evaporated and the

residue crystallised to give 5-(N-benzyl,N-phenylacetamido)-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (175d) (1.8 g; 71%) which formed yellow needles m.p. 229-231° (from ethanol-dimethylformamide), ν_{\max} 1665 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.20 (1H, d, $J_{9.5\text{Hz}}$, H-7), 8.15-8.10 (2H, m, ArH), 7.78 (1H, d, $J_{9.5\text{Hz}}$, H-8), 7.57-7.49 (3H, m, ArH), 7.11-6.89 (10H, m, ArH), 5.10 (1H, d, $J_{14\text{Hz}}$, COCH_2), 4.56 (1H, d, $J_{14\text{Hz}}$, COCH_2), 3.73 (3H, s, NCH_3), 3.44 (1H, s, ArCH_2) and 3.40 (1H, s, ArCH_2).

Found: C, 71.0; H, 4.8; N, 11.2%; ($M^+ + 1$), 505.

$\text{C}_{30}\text{H}_{24}\text{N}_4\text{O}_4$ requires: C, 71.4; H, 4.8; N, 11.1%; M, 504.

3,9-Diphenyl-1-methylpyrazino[2,3-f]quinoxaline-2,8-(1H,7H)-dione 4-N-oxide (176a)

A solution of 5-(N-methyl,N-phenylacetamido)-6-nitro-3-phenylquinoxalin-2(1H)-one (175a) (1.7 g, 0.004 mol) in Analar pyridine (20.0 ml) was stirred at 100° (water bath) and treated with 20% w/v aqueous potassium hydroxide solution (20.0 ml) and the mixture was stirred at 100° for 1h. The resulting dark solution was diluted with water (20.0 ml), filtered to remove a dark scum and acidified with concentrated hydrochloric acid to give 3,9-diphenyl-1-methylpyrazino[2,3-f]quinoxaline-2,8-(1H,7H)-dione 4-N-oxide (176a) (1.5 g; 96%) which formed yellow crystals m.p. 344-346° (decomp.) (from dimethylformamide), ν_{\max} 3200-2700 br (NH/OH) and 1680 and 1625 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.52 (1H, d, $J_{9\text{Hz}}$, H-5), 8.44-8.32 (2H, m, ArH), 7.72-7.43 (8H, m, ArH), 7.34 (1H, d, $J_{9\text{Hz}}$, H-6) and 4.24 (3H, s, NCH_3).

Found: M^+ , 396.1145.

$\text{C}_{23}\text{H}_{16}\text{N}_4\text{O}_3$ requires: M, 396.1222.

1,7-Dimethyl-3,9-diphenylpyrazino[2,3-f]quinoxalin-2,8-(1H,7H)-dione 4-N-oxide (176b)

A solution of 1-methyl-5(N-methyl,N-phenylacetamido)-6-nitro-3-phenylquinoxalin-2(1H)-one (175b) (1.4 g, 0.0033 mol) in Analar pyridine (16.5 ml) was stirred at 100° (water bath) and treated with 20% w/v aqueous potassium hydroxide solution (16.5 ml) and the mixture heated at 100° for 1h. The mixture was diluted with water (16.5 ml) and filtered to remove some gummy impurity and the filtrate acidified with concentrated hydrochloric acid to give a solid which was combined with a second crop obtained by extracting the aqueous mother liquor with methylene chloride (3x75.0 ml) and the total material (1.4 g) subjected to flash-chromatography over silica.

Elution with methylene chloride afforded the unreacted quinoxalinone (175b) (0.08 g; 6%), m.p. 225-229°C, identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with ethyl acetate then ethanol afforded 1,7-dimethyl-3,9-diphenylpyrazino[2,3-f]quinoxaline-2,8(1H,7H)-dione 4-N-oxide (176b) (total 0.61 g; 45%) which formed yellow crystals m.p. 278-280° (from ethanol-dimethylformamide), ν_{\max} 1670 and 1640 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.44-8.36 (2H, m, ArH), 8.00 (1H, d, J9Hz, H-5), 7.89-7.82 (2H, m, ArH), 7.64-7.43 (7H, m, ArH), 4.39 (3H, s, NCH_3) and 3.83 (3H, s, NCH_3).

Found: C, 70.0; H, 4.5; N, 13.6%; M^+ , 410.

$\text{C}_{24}\text{H}_{18}\text{N}_4\text{O}_3$ requires: C, 70.2; H, 4.4; N, 13.7%; M , 410.

1-Benzyl-3,9-diphenylpyrazino[2,3-f]quinoxaline-2,8(1H,7H)-dione 4-N-oxide (176c)

A solution of 5-(N-benzyl,N-phenylacetamido)-6-nitro-3-

phenylquinoxaline-2(1H)-one (175c) (2.7 g, 0.055 mol) in Analar pyridine (25.0 ml) was stirred at 100° (water bath) and treated with 20% w/v aqueous potassium hydroxide solution (25.0 ml) and the mixture was stirred at 100° for 1h. The resulting dark solution was diluted with water (25.0 ml), filtered to remove a dark scum and acidified with concentrated hydrochloric acid to give a yellow-green solid which was crystallised to afford 1-benzyl-3,9-diphenylpyrazino[2,3-f]-quinoxaline-2,8(1H,7H)-dione 4-N-oxide (176c) (1.4 g; 55%) which formed yellow crystals m.p. 330-331° (decomp.) (from water-dimethylformamide), ν_{\max} 3200-2650 br (NH/OH) and 1680 and 1640 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.62 (1H, d, J9Hz, H-5), 7.75-7.60 (3H, m, ArH), 7.52-7.35 (3H, m, ArH), 7.30-7.20 (10H, m, ArH) and 6.23 (2H, s, CH_2).

Found: M^+ , 472.1296.

$\text{C}_{29}\text{H}_{20}\text{N}_4\text{O}_3$ requires: M, 472.1535.

The aqueous dimethylformamide mother liquor was evaporated to give a dark solid (0.92 g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture, which was not further investigated.

1-Benzyl-2,8-diphenyl-6-methylimidazo[4,5-f]quinoxalin-7(6H)-one (180)

A solution of 5-(N-benzyl,N-phenylacetamido)-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (175d) (1.5 g, 0.003 mol) in Analar pyridine (15.0 ml) was stirred at 100° (water bath), treated with 20% w/v aqueous potassium hydroxide solution (15.0 ml) and the mixture maintained at 100° with stirring for 1h. The resulting solution was diluted with water (15.0

ml) and filtered to remove a dark gummy impurity. The filtrate was acidified with concentrated hydrochloric acid and extracted with methylene chloride-ethyl acetate to give a three-phase system which was filtered to afford 1-benzyl-2,8-diphenyl-6-methylimidazo[4,5-f]quinoxalin-7(6H)-one (180) (0.51 g; 35%) as yellow needles m.p. 234-235° (from ethanol-dimethylformamide), ν_{\max} 1650 br (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.13-6.96 (17H, m, ArH), 6.08 (2H, s, CH_2) and 3.80 (3H, s, NCH_3).

Found: C, 78.3; H, 5.0; N, 12.6%; M^+ , 442.

$\text{C}_{30}\text{H}_{22}\text{N}_4\text{O}_3$ requires: C, 78.7; H, 5.0; N, 12.7%; M, 442.

Evaporation of the methylene chloride-ethyl acetate mother liquor gave a yellow solid (0.79 g) m.p. 175-185° (decomp.) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture, which was not further investigated.

3,9-Diphenyl-1-methylpyrazino[2,3-f]quinoxalin-2,8(1H,7H)-dione (177a)

A suspension of 3,9-diphenyl-1-methylpyrazino[2,3-f]quinoxaline-2,8(1H,7H)-dione 4-N-oxide (176a) (0.40 g, 0.001 mol) in 20% v/v aqueous dimethylformamide (60.0 ml) was treated with sodium dithionate (0.40 g) and the suspension was heated under reflux for 1h, then treated with a second portion of sodium dithionate (0.40 g) and heating under reflux continued for a further 1h. The resulting suspension was hot filtered and the solid obtained combined with solid material which precipitated from the filtrate on cooling and stirred with hot water (5.0 ml) for 15 min, then collected to give 3,9-diphenyl-1-methylpyrazino[2,3-f]quinoxaline-2,8(1H,7H)-dione (177a) (0.18 g; 47%) which formed yellow needles m.p. >345° (from

dimethylformamide), ν_{\max} 3160 br (NH/OH) and 1670 and 1640 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.46-8.25 (4H, m, ArH), 8.01 (1H, d, J8.8Hz, H-5), 7.63-7.44 (6H, m, ArH), 7.35 (1H, d, J8.8Hz, H-6) and 4.34 (3H, s, NCH_3)

Found: C, 72.6; H, 4.2; N, 14.9%; M^+ , 380.

$\text{C}_{23}\text{H}_{16}\text{N}_4\text{O}_2$ requires: C, 72.6; H, 4.2; N, 14.7%; M , 380.

The aqueous dimethylformamide liquor was evaporated and the residue was treated with water (10.0 ml) and acidified with concentrated hydrochloric acid to give an uncharacterised solid (0.11 g) m.p. 295-300° (decomp.), ν_{\max} 3200-2700 br, w, (NH/OH) and 1655 br (CO) cm^{-1} , which defied purification on attempted crystallisation and was not further investigated.

1-Benzyl-3,9-diphenylpyrazino[2,3-f]quinoxaline-2,8(1H,7H)-dione (177c)

A solution of 1-benzyl-3,9-diphenylpyrazino[2,3-f]quinoxaline-2,8(1H,7H)-dione 4-N-oxide (176c) (0.40 g, 0.0008 mol) in 20% v/v aqueous dimethylformamide (100 ml) was treated with sodium dithionate (0.40 g) and the suspension was heated under reflux for 1h, then treated with a further portion of sodium dithionate (0.40 g) and heating under reflux continued for a further 1h. The mixture was evaporated, the residue treated with water (15.0 ml) and the solution acidified with concentrated hydrochloric acid to give 1-benzyl-3,9-diphenylpyrazino[2,3-f]quinoxaline-2,8(1H,7H)-dione (177c) (0.36 g; 93%), which formed yellow needles m.p. >340° (from ethanol-dimethylformamide), ν_{\max} 3200-2600 br (NH/OH) and 1660 (CO) cm^{-1} ,

$\delta[(\text{CD}_3)_2\text{SO}]$ 8.35-8.30 (2H, m, ArH), 8.09 (1H, d, $J_{9\text{Hz}}$, H-5), 7.81-7.78 (2H, m, ArH), 7.54-7.16 (12H, m, ArH), and 6.39 (2H, s, CH_2).

Found: C, 75.8; H, 4.4; N, 12.3%; M^+ , 456.

$\text{C}_{29}\text{H}_{20}\text{N}_4\text{O}_2$ requires: C, 76.3; H, 4.4; N, 12.3%; M , 456.

Cyanoacetyl Chloride⁷⁴

A solution of cyanoacetic acid (8.5 g, 0.1 mol) in dry ether (120 ml) was treated with phosphorus pentachloride (22 g, 0.1 mol) and the mixture was stirred at room temperature with exclusion of atmospheric moisture for 45 min. The solution was evaporated at room temperature under high vacuum (oil pump) to remove the phosphoryl chloride, leaving cyanoacetyl chloride⁷⁴ as a golden yellow oil which was used immediately without purification.

2,4-Dinitro- α -cyanoacetanilide (182b)

A solution of 2,4-dinitroaniline (18.3 g, 0.1 mol) in dry benzene (150 ml) was mixed with a solution of cyanoacetyl chloride⁷⁴ (0.2 mol) in dry benzene (50.0 ml) and the mixture was heated under reflux for 3h. The mixture was cooled and filtered to give 2,4-dinitro- α -cyanoacetanilide (182b) (25.0 g; 100%), which formed cream needles m.p. 192-193° (from ethanol-dimethylformamide), ν_{max} 3300 (NH), 2200 ($\text{C}\equiv\text{N}$), 1710 (CO) and 1500 and 1350 (NO_2) cm^{-1} , $\delta(\text{CDCl}_3)$ 11.01 (1H, s, NH), 8.73 (1H, d, $J_{2.5\text{Hz}}$, H-3), 8.55 (1H, dd, $J_{\text{ortho}} 2.5\text{Hz}$, $J_{\text{meta}} 9\text{Hz}$, H-5), 7.99 (1H, d, $J_{9\text{Hz}}$, H-6) and 4.11 (2H, s, CH_2)

Found: C, 43.1; H, 2.3; N, 22.2%; M^+ , 250.

$\text{C}_9\text{H}_6\text{N}_4\text{O}_5$ requires: C, 43.2; H, 2.4; N, 22.4%; M , 250.

The Reaction of 2,4-Dinitro-N-methylaniline with Cyanoacetyl Chloride

A solution of 2,4-dinitro-N-methylaniline (19.7 g, 0.1 mol) in dry benzene (200 ml) was treated with a solution of cyanoacetyl chloride⁷⁴ (0.2 mol) in dry benzene (50.0 ml) and the mixture was heated under reflux for 6h, then treated with a second aliquot of cyanoacetyl chloride (0.2 mol) in dry benzene (50.0 ml) and heating under reflux continued for a further 18h. The resulting suspension was hot filtered to give a red solid (3.3 g) whose t.l.c. in methylene chloride over silica showed it to be a complex mixture, which was not further investigated.

The benzene filtrate was evaporated and the residue treated with saturated aqueous sodium hydrogen carbonate solution and extracted with methylene chloride to give a solid (24.9 g) which was subjected to flash chromatography over silica.

Elution with methylene chloride afforded the unreacted 2,4-dinitro-N-methylaniline (1.4 g; 7%) m.p. 155-160°, identical (m.p. and i.r. spectrum) to an authentic sample.

Further elution with methylene chloride then with ethyl acetate afforded 2,4-dinitro-N-methyl- α -cyanoacetanilide (182c) (15.5 g; 59%), which formed cream crystals m.p. 122-123° (from ethanol-dimethylformamide), ν_{\max} 2260 (C \equiv N), 1660 (CO) and 1530 and 1345 (NO₂) cm⁻¹, δ [(CD₃)₂SO] 8.71 (1H, d, J₂₋₁H₂, H-3), 8.62 (1H, dd, J₈₋₇H₂, H-5), 7.85 (1H, d, J₈₋₇H₂, H-6), 4.35 (2H, s, CH₂) and 3.46 (3H, s, NCH₃).

Found: C, 45.2; H, 3.0; N, 21.2%; M⁺, 264.

C₁₀H₈N₄O₅ requires: C, 45.5; H, 3.1; N, 21.2%; M, 264.

Further elution with ethyl acetate then with ethanol afforded N-(2,4-dinitrophenyl)-N-methylmalonamide (187) (3.8 g; 13%) which formed cream crystals m.p. 136-137° (from ethanol-glacial acetic acid), ν_{\max} 3370 and 3170 (NH), 1690 and 1660 (CO) and 1490 and 1355 (NO₂) cm⁻¹, $\delta[(\text{CD}_3)_2\text{SO}]$ (85°) 8.77 (1H, d, J_{2.5}Hz, H-3), 8.59 (1H, dd, J_{ortho} 8.7Hz, J_{meta} 2.5Hz, H-5), 7.88 (1H, d, J_{8.7}Hz, H-6), 6.97 (1H, br s, NH₂), 3.25 (3H, s, NCH₃), 3.12 (1H, s, CH₂) and 3.06 (1H, s, CH₂).

Found: C, 42.5; H, 3.6; N, 19.7%; M⁺+1, 283.

C₁₀H₁₀N₄O₆ requires: C, 42.6; H, 3.6; N, 19.9%; M, 282.

2,4-Dinitro- α -chloroacetanilide (189a)

A solution of 2,4-dinitroaniline (18.3 g, 0.1 mol) and chloroacetyl chloride (22.6 g, 0.2 mol) in dry benzene (250 ml) was heated under reflux for 24h. The resulting solution was evaporated and the solid obtained was subjected to flash-chromatography over silica.

Elution with cyclohexane-methylene chloride (3:7) afforded a yellow solid which was crystallised to give 2,4-dinitro- α -chloroacetanilide (189a) (18.4 g; 71%) as colourless needles m.p. 112-113° (from light petroleum-toluene), ν_{\max} 3340 (NH), 1685 (CO) and 1510 and 1345 (NO₂) cm⁻¹, $\delta(\text{CDCl}_3)$ 11.66 (1H, s, NH), 9.16 (1H, d, J_{2.6}Hz, H-3), 9.08 (1H, d, J_{9.3}Hz, H-6), 8.51 (1H, dd, J_{ortho} 9.3Hz, J_{meta} 2.6Hz, H-5) and 4.29 (2H, s, CH₂).

Found: C, 37.0; H, 2.3; N, 16.2%; M⁺, 261 and 259.

C₈H₆ClN₃O₅ requires: C, 37.0; H, 2.3; N, 16.2%; M, 261 and 259.

The Attempted Reaction of 2,4-Dinitro-N-methylaniline (53b) with Chloroacetyl Chloride

A solution of 2,4-dinitro-N-methylaniline (53b) (0.99 g, 0.005 mol) in dry benzene (20.0 ml) was treated with a solution of chloroacetyl chloride (1.1 g, 0.01 mol) in dry benzene (5.0 ml) and the mixture was heated under reflux for 24h. The resulting solution was cooled and filtered to give unreacted 2,4-dinitro-N-methylaniline (53b) (0.70 g; 71%) m.p. 175-178° identical (m.p. and i.r. spectrum) to an authentic sample.

The benzene filtrate was evaporated and the residue treated with saturated aqueous sodium hydrogen carbonate solution (25.0 ml) and extracted with methylene chloride to give a solid (0.38 g) whose t.l.c. in methylene chloride over silica showed it to be a mixture containing unreacted 2,4-dinitro-N-methylaniline.

1-Hydroxy-7-nitroquinoxaline-2,3(1H,4H)-dione (183b)

(a) A solution of 2,4-dinitro- α -cyanoacetanilide (182b) (10.0 g, 0.04 mol) in 20% w/v aqueous potassium hydroxide solution (50.0 ml) was heated under reflux for 1h. The solution was acidified with concentrated hydrochloric acid to give a solid which was crystallised from ethanol-dimethylformamide to afford 1-hydroxy-7-nitroquinoxaline-2,3(1H,4H)-dione (183b) (7.2 g; 81%) as brown crystals m.p. 277-280° (decomp.), ν_{\max} 3600-3200 br (NH) and (OH), 1690 (CO) and 1540 and 1335 (NO₂) cm⁻¹, δ [(CD₃)₂SO] 12.30 (2H, br s, NH and OH), 8.02 (1H, d, J_{2,5} 2.5Hz, H-8), 8.00 (1H, dd, J_{ortho} 8.3Hz, J_{meta} 2.5Hz, H-6) and 7.34 (1H, d, J_{8,5} 8.3Hz, H-5).

Found: M^+ , 223.0228.

$C_8H_5N_3O_5$ requires: M , 223.0229.

(b) A suspension of 2,4-dinitro- α -cyanoacetanilide (182b) (0.50 g, 0.002 mol) in absolute ethanol (5.0 ml) was treated with a solution of sodium (0.18 g, 0.008 g.atom) in absolute ethanol (5.0 ml) and the mixture heated under reflux for 1h. The solution was evaporated and the residue treated with water (5.0 ml) to give a dark intractable solid (0.45 g) m.p. $>330^\circ$, whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture from which no identifiable material could be obtained.

(c) A solution of 2,4-dinitro- α -cyanoacetanilide (182b) (2.5 g, 0.01 mol) in Analar pyridine (10.0 ml) was treated with aqueous 1M sodium hydroxide (10.0 ml) and the mixture was stirred at room temperature for 1h. Dilution with water (20.0 ml), acidification with concentrated hydrochloric acid, followed by neutralisation with solid sodium acetate afforded a solid, which crystallised from ethanol-dimethylformamide to give the unreacted cyanoacetanilide (182b) (0.97 g; 39%), m.p. $173-176^\circ$ (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The ethanolic filtrate was evaporated to give a brown solid (1.2 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture, which was not further investigated.

1-Hydroxy-4-methyl-7-nitroquinoxaline-2,3(1H,4H)-dione (183c)

(a) A suspension of 2,4-dinitro- N -methyl- α -cyanoacetanilide (182c) (0.50 g, 0.002 mol) in absolute ethanol (5.0 ml) was mixed with a solution of sodium (0.18 g, 0.008 g.atom) in

absolute ethanol (5.0 ml) and the mixture was heated under reflux for 1h. The solution was evaporated and the residue treated with water (5.0 ml), acidified with concentrated hydrochloric acid and extracted with ethyl acetate to give 1-hydroxy-4-methyl-7-nitroquinoxaline-2,3(1H,4H)-dione (183c) monohydrate (0.27 g; 57%) which formed brown crystals m.p. 235-236° (decomp.) (from ethanol), ν_{\max} 3580 and 3350 br (OH), 1680 (CO) and 1525 and 1340 (NO₂) cm⁻¹, $\delta[(\text{CD}_3)_2\text{SO}]$ 8.22 (1H, d, J2.2Hz, H-8), 8.14 (1H, dd, J_{ortho} 8.8Hz, J_{meta} 2.2Hz, H-6), 7.63 (1H, d, J8.8Hz, H-5) and 3.58 (3H, s, NCH₃).

Found: C, 42.7; H, 3.5; N, 16.5%; M⁺, 237.

C₉H₇N₃O₅.H₂O requires: C, 42.4; H, 3.5; N, 16.5%; (M-H₂O), 237.

(b) A solution of 2,4-dinitro-N-methyl- α -cyanoacetanilide (182c) (1.1 g, 0.004 mol) in 20% w/v aqueous potassium hydroxide (5.0 ml) was heated under reflux for 1h. The solution was acidified with concentrated hydrochloric acid to give a solid which was heated under reflux in ethanol (75.0 ml) and hot filtered to remove inorganic material. The ethanolic filtrate was evaporated to give a brown solid (0.52 g) whose t.l.c. in methylene chloride over silica showed it to be a close running mixture from which no characterisable material could be obtained.

The aqueous mother liquor was extracted with ethyl acetate to give an intractable gummy brown solid (0.11 g) whose t.l.c. in ethanol showed it to be a multicomponent mixture which was not further investigated.

(c) A solution of 2,4-dinitro-N-methyl- α -cyanoacetanilide (182c) (0.50 g, 0.002 mol) in Analar pyridine (2.0 ml) was

stirred at room temperature and treated with aqueous 1M sodium hydroxide (2.0 ml) and the mixture was stirred at room temperature for 1h. The solution was diluted with water (4.0 ml) and acidified with concentrated hydrochloric acid to give a brown solid (0.20 g) whose t.l.c. in ethanol over silica showed it to be a multicomponent mixture, which was not further investigated.

The aqueous acidic filtrate was extracted with ethyl acetate to afford an orange solid (0.27 g) whose t.l.c. in ethanol over silica showed it to be a complex mixture, which was not further investigated.

The Attempted Reaction of 2,4-Dinitro- α -chloroacetanilide (189a) with Pyridine

A solution of 2,4-dinitro- α -chloroacetanilide (189a) (0.5 g, 0.002 mol) in Analar pyridine (5.0 ml) was heated under reflux for 10 min. The resulting dark solution was evaporated to give a dark intractable glassy solid (0.66 g) m.p. 165-170°, whose t.l.c. in ethanol over silica showed it to be a close running mixture which was not further investigated.

The Attempted Reaction of 1-Hydroxy-7-nitroquinoxaline 2,3(1H,4H)-dione (183b) with Acetyl Chloride in Glacial Acetic Acid

A suspension of 1-hydroxy-7-nitroquinoxaline 2,3(1H,4H)-dione (183b) (1.8 g, 0.008 mol) in acetyl chloride (20.0 ml) and glacial acetic acid (12.0 ml) was heated under reflux for 72h. The resulting suspension was hot filtered to remove some dark intractable solid and the filtrate was evaporated to

give a solid tentatively formulated as 1-acetoxy-7-nitroquinoxaline-2,3(1H,4H)-dione (188) (1.1 g; 49%) m.p. 180-185° (decomp.), ν_{\max} 3680-2600 br (NH/OH), 1810 and 1720 (CO) and 1535 and 1340 (NO₂) cm⁻¹.

The N-acetoxy derivative (188) was converted, on attempted crystallisation from aqueous dimethylformamide, into the starting N-hydroxyquinoxalinedione (183b) m.p. 260-265° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample, which was also obtained by heating the crude N-acetoxy derivative (188) with aqueous 2M sodium hydroxide for a few min. followed by acidification with concentrated hydrochloric acid.

5-Chloro-6-nitroquinoxaline-2,3(1H,4H)-dione (186b)

A solution of 1-hydroxy-7-nitroquinoxaline-2,3(1H,4H)-dione (183b) (2.2 g, 0.01 mol) and toluene-*p*-sulphonyl chloride (4.2 g, 0.022 mol) in dry dimethylformamide (50.0 ml) was heated at 100° (water bath) for 2h. The solution was evaporated and the residue treated with water (50.0 ml) to give a solid which was treated with aqueous 2M sodium hydroxide (10.0 ml) and animal-charcoal and the suspension filtered through kieselguhr. The filtrate was acidified with concentrated hydrochloric acid and filtered to remove some dark intractable solid (0.58 g) m.p. >330°, extraction of the filtrate with ethyl acetate afforded a gummy solid (0.08 g) whose t.l.c. in ethanol over silica showed it to be a complex mixture which was not further investigated.

The aqueous mother liquor was extracted with ethyl acetate to give 5-chloro-6-nitroquinoxaline-2,3(1H,4H)-dione (186b)

(1.1 g; 45%) which formed cream crystals m.p. 221-223° (from ethanol-dimethylformamide), ν_{\max} 3580-3250 br (NH), 3250-2500 br, w (OH), 1700 br and 1650 br (CO) and 1535 and 1340 (NO_2) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 12.14 (2H, br, NH), 7.83 (1H, d, J8.8Hz, H-7) and 7.19 (1H, d, J8.8Hz, H-8).

Found: 240.9882.

$\text{C}_8\text{H}_4^{35}\text{ClN}_3\text{O}_4$ requires: 240.9890.

Found: 242.9878.

$\text{C}_8\text{H}_4^{37}\text{ClN}_3\text{O}_4$ requires: 242.9861.

8-Phenyl-1,2,5-oxadiazolo[3,4-f]quinoxalin-7(6H)-one
3-N-Oxide (159a)

A solution of 5-chloro-6-nitro-3-phenylquinoxalin-2(1H)-one (122b) (6.0 g, 0.02 mol) and sodium azide (2.0 g, 0.03 mol) in dimethylformamide (40.0 ml) and water (4.0 ml) was heated under reflux for 1h. The solution obtained was evaporated, the residue treated with water (20.0 ml) and acidified with aqueous 2M hydrochloric acid (20.0 ml) to give a solid which was collected and crystallised from glacial acetic acid-dimethylformamide, then washed with ethanol, to give 8-phenyl-1,2,5-oxadiazolo[3,4-f]quinoxalin-7(6H)-one 3-N-oxide (159a) (2.9 g; 52%) as yellow-brown crystals m.p. 295-298° (from glacial acetic acid-dimethylformamide), ν_{\max} 3200-2700 br (NH/OH), 1660 (CO) and 1620 (C=N) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.46-8.33 (2H, m, ArH), 7.66 (1H, d, J10Hz, H-4), 7.58-7.44 (3H, m, ArH) and 7.29 (1H, d, J10Hz, H-5).

Found: C, 59.3; H, 3.1; N, 19.7%; M^+ , 280.0596.

$\text{C}_{14}\text{H}_8\text{N}_4\text{O}_3$ requires: C, 60.0; H, 2.9; N, 20.0%; M , 280.0596.

The glacial acetic acid filtrate was evaporated to give a dark solid (3.0 g) whose t.l.c. in ether over silica showed it to be a multicomponent mixture, which was not further investigated.

8-Phenyl-1,2,5-oxadiazolo[3,4-f]quinoxalin-7(6H)-one (160)

A solution of 8-phenyl-1,2,5-oxadiazolo[3,4-f]quinoxalin-7(6H)-one 3-N-oxide (159a) (0.56 g, 0.002 mol) in aqueous 2M sodium hydroxide (5.0 ml) was treated with a solution of sodium dithionate (1.1 g) in water (5.0 ml) and the mixture was stirred at room temperature for 3h. Acidification with concentrated hydrochloric acid afforded 8-phenyl-1,2,5-oxadiazolo[3,4-f]quinoxalin-7(6H)-one (160) (0.51 g; 96%), which formed brown crystals m.p. 298-301° (decomp.) (from dimethylformamide-water), ν_{\max} 3200-2700 br (NH/OH) and 1660 (CO) cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 8.53-8.31 (2H, m, ArH), 8.16 (1H, d, J9.5Hz, H-4) and 7.65-7.37 (4H, m, ArH).

Found: M^+ , 264.0643.

$\text{C}_{14}\text{H}_8\text{N}_4\text{O}_2$ requires: M , 264.0647.

The Attempted Reaction of 5-Chloro-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (149) with Sodium Azide

A hot solution of 5-chloro-1-methyl-6-nitro-3-phenylquinoxalin-2(1H)-one (149) (0.63 g, 0.002 mol) in dimethylformamide (5.0 ml) and water (0.5 ml) was treated with sodium azide (0.20 g, 0.003 mol) and the mixture was heated under reflux for 1h. The solution obtained was diluted with water (15.0 ml) to give an intractable brown solid (0.32 g) m.p. 105-110° (decomp.) whose t.l.c. in ether over silica showed

it to be a multicomponent mixture from which no identifiable material could be obtained.

Workup of the aqueous mother liquor gave only a series of gums (total 0.15 g) whose t.l.c. in ether over silica showed them to be complex mixtures, which were not further investigated.

The Attempted Methylation of 8-Phenyl-1,2,5-oxadiazolo[3,4-f]-quinoxalin-7(6H)-one 3-N-Oxide (159a)

(a) A suspension of 8-phenyl-1,2,5-oxadiazolo[3,4-f]-quinoxalin-7(6H)-one 3-N-oxide (159a) (0.56 g, 0.002 mol) and anhydrous potassium carbonate (1.5 g) in Analar acetone (50.0 ml) was treated with dimethyl sulphate (1.0 ml) and the mixture was heated under reflux for 4h. The resulting suspension was evaporated, the residue treated with water (10.0 ml) and the insoluble solid collected to afford impure unreacted oxadiazoloquinoxalinone (159a) (0.50 g; 89%) m.p. 215-220° (decomp.) identical (i.r. spectrum) to an authentic sample.

(b) A solution of 8-phenyl-1,2,5-oxadiazolo[3,4-f]-quinoxalin-7(6H)-one 3-N-oxide (159a) (0.56 g, 0.002 mol) in aqueous 2M sodium hydroxide (10.0 ml) was treated dropwise at room temperature with dimethyl sulphate (2.0 ml) and the mixture was shaken mechanically for 1h. A further portion of aqueous 2M sodium hydroxide (5.0 ml) was then added and the mixture was shaken at room temperature for a further 1h. The resulting solution was extracted with ethyl acetate to give a three-phase system which was filtered to give a solid (0.30 g) m.p. 225-227° (decomp.) whose t.l.c. in toluene over silica

showed it to be a close running complex mixture which was not further investigated.

Evaporation of the ethyl acetate extract afforded a glassy brown solid (0.26 g) whose t.l.c. in toluene over silica showed it to be a complex mixture which was not further investigated.

The Attempted Reaction of 8-Phenyl-1,2,5-oxadiazolo[3,4-f]-quinoxalin-7(6H)-one 3-N-Oxide (159a) with Formaldehyde in the Presence of Aqueous Methanolic Potassium Hydroxide

A suspension of 8-phenyl-1,2,5-oxadiazolo[3,4-f]quinoxalin-7(6H)-one 3-N-oxide (159a) (0.56 g, 0.002 mol) in methanol (2.5 ml) and water (2.5 ml) was stirred and treated at room temperature with 40% aqueous formaldehyde solution (0.15 g), followed by a solution of potassium hydroxide (0.25 g) in water (1.0 ml) and methanol (1.0 ml) and the resulting mixture was stirred at 40-50° (water bath) for 1h. The dark solution obtained was treated with water (5.0 ml) and acidified with concentrated hydrochloric acid to give the unreacted oxadiazoloquinoxalinone (159a) (yield quantitative) m.p. 280-283° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Base-catalysed Reaction of 8-Phenyl-1,2,5-oxadiazolo[3,4-f]quinoxalin-7(6H)-one 3-N-Oxide (159a) with Acetylacetone

(a) A solution of 8-phenyl-1,2,5-oxadiazolo[3,4-f]quinoxalin-7(6H)-one 3-N-oxide (159a) (0.56 g, 0.002 mol) in dry dimethylformamide (10.0 ml) was treated with acetylacetone

(0.20 g, 0.002 mol) and triethylamine (0.80 g, 0.008 mol) and the mixture was stirred at room temperature for 16h. The resulting dark solution was evaporated and the residue was treated with water (5.0 ml) to give the unreacted oxadiazoloquinoxalinone (159a) (0.55 g; 98%) m.p. 274-277° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

(b) A solution of 8-phenyl-1,2,5-oxadiazolo[3,4-f]-quinoxalin-7(6H)-one 3-N-oxide (159a) (0.56 g, 0.002 mol) and acetylacetone (0.22 g, 0.0022 mol) in dry dimethylformamide (10.0 ml) was treated dropwise with stirring with piperidine (0.37 g, 0.0044 mol) and the resulting mixture was stirred at room temperature for 16h. The solution was evaporated, the residue treated with water (5.0 ml) and the suspension obtained acidified with concentrated hydrochloric acid. Extraction with ethyl acetate and filtration of the resulting three-phase system afforded impure unreacted oxadiazoloquinoxalinone (159a) (0.54 g; 96%) m.p. 230-235° (decomp.) identical (i.r. spectrum) to an authentic sample.

The Attempted Reduction of 8-Phenyl-1,2,5-oxadiazolo[3,4-f]-quinoxalin-7(6H)-one 3-N-Oxide (159a) with Sodium Borohydride in Diethylene Glycol Dimethyl Ether

A solution of sodium borohydride (0.1 g) in diethylene glycol dimethyl ether (5.0 ml) was stirred and treated with portions of 8-phenyl-1,2,5-oxadiazolo[3,4-f]quinoxalin-7(6H)-one 3-N-oxide (159a) (0.56 g, 0.002 mol) over 20 min. The mixture was cooled (ice bath), diluted with water (25.0 ml),

then acidified with glacial acetic acid to give a solid which was washed with ethanol to afford the unreacted oxadiazoloquinoxalinone (159a) (0.42 g; 75%) m.p. 280-285° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample.

Workup of the aqueous mother liquor afforded no further identifiable material.

A P P E N D I X

• General Experimental Details

Infrared spectra were recorded from nujol suspension or thin films using Perkin Elmer 157G, Perkin Elmer 298 or Perkin Elmer 781 spectrophotometers. I.r. bands were strong and sharp unless otherwise specified as (w = weak) and (br = broad).

^1H n.m.r. spectra were recorded for solutions in the specified solvents at 80MHz using a Bruker WP-80 instrument, at 100MHz using a Varian HA-100 instrument, at 200MHz using a Bruker WP-200 instrument, or at 360MHz using a Bruker WH-360 instrument. Signals were sharp singlets unless otherwise specified as (br = broad) and (s = singlet), (d = doublet), (t = triplet), (q = quartet), and (m = multiplet). Tetramethylsilane, dimethyl sulphoxide, and chloroform were used as internal standards depending on the instrument and the solvent used for recording spectra. ^{13}C n.m.r. spectra were recorded for solutions in the specified solvents using a Varian CFT-20 instrument.

Routine mass spectra and accurate masses were measured at 70eV on an A.E.I. MS-902 instrument.

Microanalyses were determined by Mr. J. Grunbaum, Department of Chemistry, University of Edinburgh. All melting-points were determined on a Koffler hot-stage and are uncorrected.

Crude solid products isolated by filtration from reaction mixtures were dried in vacuo at room temperature unless otherwise stated. All organic extracts were dried over anhydrous magnesium sulphate prior to evaporation under reduced pressure. Solvents were of technical grade unless otherwise specified

and except where stated light petroleum had b.p. 60-80°.

Thin layer chromatography (t.l.c.) was carried out over silica (Merck 7730 Kieselgel GF-254, type 60) or alumina (Merck 1068 GF-254, type E). Column chromatography was carried out over silica (Fisons 80-200 mesh) or alumina (Spence type H, activity III). Flash column chromatography was conducted at 5-7 p.s.i. (air line) over silica (Merck 9385 Kieselgel, type 60).

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